IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA LTD., and VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA FRANCE S.A.S.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 18-390-MN
TEVA PHARMACEUTICALS USA, INC.,	)	
Defendants.	)	

DEFENDANT'S CORRECTED PROPOSED FINDINGS OF FACT REGARDING INVALIDITY

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TABLE OF ABBREVIATIONS AND KEY TECHNICAL TERMS

’251 patent	U.S. Patent No. 9,561,251 (JTX-0001)
’442 patent	U.S. Patent No. 6,714,442 (JTX-0003)
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
Asserted Claims	Claims 29, 30, 33, and 56 of U.S. Patent No. 9,561,251 (the “’251 patent”)
Auryxia	Ferric citrate phosphate binder indicated for the control of serum phosphorus levels in adult patients with chronic kidney disease on dialysis (DTX-0317)
CKD	Chronic Kidney Disease
DS	Drug Substance
ESRD	End-Stage Renal Disease
Example 1 Composition	The composition recited in Example 1 of U.S. Patent No. 6,174,442 (the “’442 patent”) at 3:30-51
FDA	Food and Drug Administration
Fosrenol	Lanthanum carbonate phosphate binder indicated for the reduction of serum phosphorus in patients with end stage renal disease (PTX-0544)
Hergesell	The 1999 article from Nephrology Dialysis Transplantation entitled “Stabilized polynuclear iron hydroxide is an efficient oral phosphate binder in uraemic patients,” written by Olaf Hergesell and Eberhard Ritz (JTX-0007)
Lieberman	Volume 1 of the book entitled “Pharmaceutical Dosage Forms: Tablets,” by H. Lieberman and L. Lachman, and published in 1980.
NDA	New Drug Application
PA21	The composition tested in U.S. Patent No. 6,174,442 (the “’442 patent”) and the Hergesell study (JTX-0007)
Phoslyra	Calcium acetate phosphate binder indicated for the reduction of serum phosphorus in patients with end stage renal disease (PTX-0211)
POSA	Person of Ordinary Skill in the Art
Renagel	Sevelamer hydrochloride phosphate binder indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis (PTX-0214)
Renvela	Sevelamer carbonate phosphate binder indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis (DTX-0120; PTX-0217)

I. THE ASSERTED PATENT

1. Plaintiffs assert that Teva infringes claims 29, 30, 33, and 56 of U.S. Patent No. 9,561,251 (the "'251 patent") (JTX-001). (D.I. 277-1 ("Uncontested Facts") at ¶ 6.)

2. The '251 patent, entitled "Pharmaceutical compositions," was filed on May 14, 2010 and issued on February 7, 2017. (JTX-0001.1.)

3. The named inventors on the '251 patent are Ludwig Daniel Weibel and Erik Philipp. (Uncontested Facts at ¶ 7.)

4. The '251 patent claims priority to PCT/EP2008/065444 filed on November 13, 2008, which claims priority to European Patent No. 07120837 filed on November 16, 2007. (Uncontested Facts at ¶ 8.)

5. On August 13, 2019 the United States Patent Office Issued a Certificate of Correction providing "In Claim 23, at Column 16, Line 56, "claim 11" should read --claim 22--. (Uncontested Facts at ¶ 9.)

6. According to the '251 patent, the alleged "invention relates to pharmaceutical compositions comprising iron oxy-hydroxide in high loading in a form suitable for oral administration." (JTX-0001 at 1:5-7.) Further, the '251 patent specification indicates that "high loading" means that "the iron oxy-hydroxide is present in an amount of 10 to 80% (w/w)," and suitable dosage forms include "tablets and pills . . . chewable forms, dry powders, granules, capsules or sachets containing these, granules, wafers, films, lozenges, and the like." (JTX-0001 at 5:31-32, 8:44-52; Tr. 322:8-13, 364:13-18.)

7. The '251 patent teaches that two of the features common to the allegedly inventive compositions are: (1) "a low iron release rate of below 2.5% w/w, which is essential for phosphate adsorbers"; and (2) iron oxy-hydroxides that "due to their chemical nature . . . essentially are not

absorbed by the human body, i.e. they are essentially non-bioabsorbable." (JTX-0001 at 3:6-7, 4:64-67; Tr. 326:4-15.)

8. According to the '251 patent, the content of iron oxy-hydroxide is calculated as approximately 1.6 times the content of iron. (JTX-0001 at 5:34-37; Uncontested Facts at ¶ 32.)

9. In the Background section, the '251 patent admits that stabilized iron oxy-hydroxides had already been shown to have "superior phosphate adsorption capacity" and to be "efficient oral phosphate binders for the treatment of hyperphosphatemia," as reflected in "EP 0 868 125" and "Nephrol. Dial. Transplant 14, 863, 1999." (JTX-0001 at 1:27-37; Tr. 322:14-323:9.) European Patent No. EP 0 868 125 contains the same disclosure as U.S. Patent No. 6,174,442 (Uncontested Facts at ¶ 30; Tr. 323:10-14), Defendant's primary prior art reference. Further, Defendant has also asserted the cited Nephrology Dialysis Transplantation publication, "Stabilized Polynuclear Iron Hydroxide is an Efficient Oral Phosphate Binder in Uraemic Patients" by Olaf Hergesell & Eberhard Ritz. (Uncontested Facts at ¶ 26; Tr. 323:5-9, 330:24-331:6.)

II. WITNESSES

A. Defendant's Expert Witnesses

10. Defendant called three expert witnesses live at trial: Dr. Stephen Z. Fadem, Dr. Walter G. Chambliss, and Dr. DeForest McDuff.

11. Dr. Fadem is a medical doctor and a clinical professor who specializing in nephrology at Baylor College of Medicine and the DeBakey Veterans Administration Hospital in Houston, Texas. (Tr. 206:18-207:19.) Dr. Fadem has been practicing for over 42 years, which includes treating patients with CKD and with various therapies available during this time, including in 2008. (Tr. 207:20-208:1, 210:10-20.) He is the medical director of several dialysis units, including one of the nation's largest units, and he treats hundreds of patients, most of whom

have hyperphosphatemia. (Tr. 209:14-210:17.) Dr. Fadem has authored and edited over 50 peer-reviewed papers and book chapters, as well as over 25 patient education articles. (Tr. 208:10-23.) He also has served in leadership positions for professional associations focused on nephrology, including as the Vice President and Chair of the Medical Advisory Board for the American Association of Kidney Patients, as well as the current Chair of the Medical Advisory Board of the National Kidney Foundation in Houston. (Tr. 208:24-209:13.) Teva offered and this Court accepted Dr. Fadem as an expert in the diagnosis and treatment of patients that have chronic kidney disease (CKD), including patients that are on dialysis. (Tr. 210:21-211:3.)

12. Dr. Chambliss is a Professor Emeritus of Pharmaceutics and Drug Delivery and a Research Professor Emeritus in the Research Institute of Pharmaceutical Sciences at the University of Mississippi, where he teaches courses on pharmaceutical formulation, pharmaceutical manufacturing, and pharmaceutical industry regulations. (Tr. 278:2-279:13.) Dr. Chambliss is the author of 40 publications and several book chapters. (Tr. 280:3-12.) He also has served on the International Steering Committee for the *Handbook of Pharmaceutical Excipients*, which is an internationally recognized reference in the pharmaceutical industry that describes excipients and their properties. (Tr. 280:3-17.)

13. Dr. Chambliss has over 40 years of research experience involving oral suspensions and solid dosage forms, including chewable tablets, phosphate binders that were heavily used throughout the 1980s and early 1990s (including aluminum hydroxide, magnesium hydroxide, and calcium carbonate), and relevant inactive ingredients (including saccharose and starch). (Tr. 281:22-282:7, 284:11-285:2.) Over the course of his career, Dr. Chambliss has been involved in the development of over 300 drug products, including chewable tablets containing iron, chewable tablets containing phosphate binders, high load antibiotic powders, and oral suspensions

containing phosphate binders. (Tr. 283:21-284:10.) Dr. Chambliss began his career at GD Searle Pharmaceutical Company, where he was responsible for the development of solid oral dosage forms, including a sprinklable formulation that children ingested with food. (Tr. 282:12-20.) Dr. Chambliss also worked at Bristol Myers, where he was in management and development of antibiotic formulations, including powders for suspension in water and subsequent oral administration. (Tr. 282:21-283:2.) Dr. Chambliss also worked at Schering-Plough, where he was involved in developing many chewable tablets, including chewable tablets that comprised high doses of phosphate binders and weighed up to five grams. (Tr. 281:22-282:7, 283:3-11, 325:16-326:3, 338:23-339:3, 339:23-24.) While at Schering-Plough, Dr. Chambliss rose from being an associate director in charge of formulation development to being vice president and, for a time, interim medical director. (Tr. 283:3-6.) Dr. Chambliss meets both parties' definitions of a person of ordinary skill in the art. (Tr. 287:7-20.) Teva offered and this Court accepted Dr. Chambliss an expert in pharmaceutical science and formulation. (Tr. 285:10-16.)

14. Dr. McDuff is an economic consultant at Insight Economics, which he co-founded in 2017. (Tr. at 742:10-743:4.) He has a Ph.D. in economics from Princeton University and serves as adjunct faculty in the Department of Economics at the University of North Carolina, Chapel Hill. (*Id.*) Dr. McDuff has substantial experience in the pharmaceutical industry, including more than 50 cases considering commercial success, and has published several articles on this topic. (*Id.*) Teva offered and this Court accepted Dr. McDuff as an expert in economics and commercial success. (Tr. 743:5-10.)

B. Plaintiffs' Expert Witnesses

15. Plaintiffs called four expert witnesses live at trial: Dr. Adam Myers, Dr. Anjay Rastogi, Dr. Robert Williams III, and Ms. Carla Mulhern.

16. Dr. Myers is a senior project manager at Evonik Corporation and president of Coldbrook consulting. (Tr. 142:11-16.) Plaintiffs offered and this Court accepted Dr. Myers as an expert in evaluation of drug performance and, in particular, dissolution testing and analysis. (Tr. 144:5-9.)

17. Dr. Rastogi is the Chief of Nephrology in the UCLA Health Department of Medicine. (Tr. 77:13-20.) Plaintiffs offered and this Court accepted Dr. Rastogi as an expert in pharmacology, nephrology, and the treatment of hyperphosphatemia. (Tr. 88:10-16.)

18. Dr. Williams is a professor of pharmacy at the University of Texas Austin College of Pharmacy. (Tr. 644:4-6.) Plaintiffs offered and this Court accepted Dr. Williams as an expert in the design and development of pharmaceutical formulations. (Tr. 645:15-22.)

19. Ms. Mulhern is a managing principal at Analysis Group, an economic and financial consulting firm. (Tr. 561:22-562:13.) Plaintiffs offered and this Court accepted Ms. Mulhern as an expert in economics. (Tr. 564:6-11.)

C. Witnesses Appearing by Deposition

20. Defendant called three fact witnesses by deposition: Dr. Erik Philipp, Dr. Laurent Chofflon, and Mr. Charles DeLoach. Dr. Philipp is a named inventor on the ’251 patent and the prior art ’442 patent. (Tr. 231:3-18.) Dr. Philipp has been employed by Vifor Pharma since 1991 and was designated by Plaintiffs as a Rule 30(b)(6) witness. (Tr. 229:1-9, 229:23-231:1.) Dr. Chofflon is an employee of Vifor involved in the pharmaceutical development finished products, including testing relating to the active pharmaceutical ingredient in Vifor’s PA21 project, and was designated by Plaintiffs as a Rule 30(b)(6) witness. (Tr. 268:2-23.) Mr. DeLoach was Plaintiffs’ Rule 30(b)(6) witness. (Tr. 728:6-8.)

21. Plaintiffs listed Dr. Wesley Harris as an expert witness who they may call.

However, Dr. Harris never testified at trial even though Dr. Williams and Ms. Mulhern relied upon Dr. Harris's opinions. (*See* D.I. 277-8.)

III. PERSON OF ORDINARY SKILL IN THE ART

22. The subject matter of the '251 patent falls within the field of pharmaceutical sciences. A POSA at the relevant time would have possessed at least a Bachelor's degree, and more likely a Master's or Doctoral degree, in the field of pharmaceutical sciences or a related discipline, and several years of experience formulating dosage forms containing pharmaceutically active compounds. A POSA could have a lower level of formal education if such person had a higher degree of experience. Furthermore, because drug discovery and development is a multidisciplinary effort, a POSA might interface or consult with individuals having specialized expertise such as, for example, a physician with experience in the administration, dosing, and efficacy of drugs for treating hyperphosphatemia.

IV. CLAIM CONSTRUCTION

23. The Court has construed the phrase "essentially non-bioabsorbable" (recited in asserted claim 29) to mean "[u]pon oral administration, the iron oxy-hydroxide is not absorbed by the human body in a clinically significant amount." (D.I. 115 at 2; Tr. 344:19-345:4.)

24. The Court has construed the phrase "iron release rate below 2.5% w/w" (recited in asserted claim 30) to mean "[t]he iron release measured in water at a pH of 3 according to European Pharmacopeia chapter 2.9.3 using standard dissolution equipment and parameters as described in the monograph, where iron content is analyzed by titration after 2 hours, wherein the quantity of iron dissolved after 2 hours is less than 2.5% w/w." (D.I. 115 at 2; Tr. 354:24-355:13.)

V. THE PRIOR ART ASSERTED AT TRIAL

25. At trial, Defendant argued that the asserted claims are invalid as obvious in view of

the following references:

a. U.S. Patent No. 6,174,442 (the "'442 patent") (JTX-0003);

b. Olaf Hergesell & Eberhard Ritz, Stabilized Polynuclear Iron Hydroxide is an Efficient Oral Phosphate Binder in Uraemic Patients, 14 NEPHROLOGY DIALYSIS TRANSPLANTATION 863 (1999) ("Hergesell") (JTX-0007);

c. U.S. Patent No. 4,970,079 (the "'079 patent") (JTX-0005);

d. PHARMACEUTICAL DOSAGE FORMS: TABLETS, VOL. 1, edited by H. Lieberman and L. Lachman, Marcel Dekker, Inc., New York (1980) at 68-98, 109-184, 289-337 ("Lieberman") (JTX-0008); and

e. U.S. Patent No. 7,465,465 (the "'465 patent") (JTX-0004).

(Tr. 287:21-288:14.)

26. Each of these references qualifies as prior art to the '251 patent under 35 U.S.C. §§ 102 and 103. (Uncontested Facts at ¶ 26; Tr. 288:15-17.)

A. The '442 Patent

27. The '442 patent issued on January 16, 2001 from U.S. Patent Application No. 09/077,944, which claims foreign priority to European Application No. EP 9605695 (the "'695 application") filed on December 19, 1996. The '695 application claims priority to German Patent Application No. DE 195 47 356 (the "'356 application") filed on December 19, 1995. The '695 application published as International Patent Publication No. WO97/22266 (the "'266 publication") on June 26, 1997, and the '356 application published on that same date.

28. The '442 patent identifies Vifor (International) AG as the assignee and Peter Geisser and Erik Philipp as the inventors. (JTX-0003.1.)

29. The ’442 patent contains the same disclosure as EP 0 868 125 (Uncontested Facts at ¶ 30), which is repeatedly discussed throughout the specification of the ’251 patent with regard to stabilized iron oxy-hydroxide compositions. (JTX-0001 at 1:27-37, 2:57-62, 3:38-47, 4:39-42, 4:45-63.)

30. The ’442 patent also contains the same disclosure as the ’356 application, which is cited in Hergesell as reference [13]. (Uncontested Facts at ¶ 31.) Specifically, Hergesell directs the reader to reference [13] for “[f]urther product information” regarding the “insoluble polynuclear iron(III)-hydroxide” that was used in the study (JTX-0007.3; Tr. 306:6-22.) Dr. Philipp, an inventor named on the ’442 patent, confirmed that Hergesell referred the reader to the ’442 patent for further production information. (Tr. 245:10-17.) According the ’251 patent, Hergesell demonstrated that stabilized iron oxy-hydroxide phosphate binders are “efficient oral phosphate binders in the treatment of hyperphosphataemia.” (JTX-0001 at 1:27-37.)

31. According to Dr. Chambliss, Defendant’s technical expert, the ’442 patent generally discloses an iron oxy-hydroxide phosphate binder that, among other things: (1) is particularly suitable for oral administration; (2) is stabilized with carbohydrates; (3) has a high load of iron and iron oxy-hydroxide; (4) is insoluble; (5) has low iron release; (6) has superior phosphate adsorption capacity; (7) can be formulated “as such” (i.e., without additional excipients) or together with customary inactive ingredients; (8) can be formulated in a number of different dosage forms, including powders and tablets; and (9) has a preferred dose of 800 mg iron oxy-hydroxide administered three times per day with meals. (Tr. 290:5-292:1; *see also* JTX-0003 at 1:5-10, 16-19, 1:42-47, 1:52-58, 1:66-2:27, 2:58-62, 3:9-21, claim 12.)

32. Example 1 of the ’442 patent specifically disclosed a powder consisting of iron oxy-hydroxide stabilized with saccharose and starch, wherein the powder comprised high loading

amounts of iron (21.2% by weight) and iron oxy-hydroxide (33.92% by weight). (JTX-0003 at 3:30-50; Tr. 290:5-291:6, 295:4-15.)

33. Dr. Philipp, a named inventor on both the ’251 and ’442 patents, confirmed that Example 1 of the ’442 patent corresponds to the drug substance that was administered in the Hergesell study, initially designated by Plaintiffs as PA21, and later designated as PA21-1. (Tr. 243:17-242:2, 253:5-255:6, 259:18-24.) As Vifor’s 30(b)(6) witness Dr. Chofflon confirmed, the only difference in composition between PA21-1 and the later PA21-2 was the inclusion of pregelatinized starch in PA21-2. (Tr. (Chofflon) 271:3-7.)

34. Dr. Philipp also authored an article indicating that the patients in the Hergesell study (reference 18) “were given PA21.” (DTX-0062.0007-8). Plaintiffs’ internal documents and regulatory submissions further confirm that PA21 (now referred to as PA21-1) was disclosed in the ’442 patent and administered in the Hergesell study. (DTX-0063.0017-19, 0063 (discussing the results reported in Hergesell with respect to PA21 and indicating that PA21’s phosphate binding capacity was shown in reference 9, which is the ’356 application corresponding to the ’442 patent); DTX-0076.0013, 0069 (indicating that PA21-1 was investigated in an “Investigator-initiated study [3],” which is Hergesell.)

35. Examples 2 through 5 of the ’442 patent describe the results of studies designed to determine the phosphate binding capacity of the Example 1 material at three different pH values (3.0, 5.5, and 8.0). (JTX-0003 at 3:30-5:23.)

36. Examples 6 through 9 of the ’442 patent describe the results of studies designed to determine the phosphate binding capacity of adsorbent materials made by adding 30.0 g of saccharose (Example 6), amylopectin (Example 7), white dextrin (Example 8), or humic acid (Example 9), to an iron oxy-hydroxide suspension prepared in accordance with Example 1. (JTX-

0003 at 5:24-6:44.)

37. Examples 10 and 11 of the ’442 patent describe the result of studies designed to determine the binding capacities of “commercially available iron(III) oxides” (Example 10) and non-stabilized α-, β-, and γ-iron oxy-hydroxides. (JTX-0003 at 6:48-8:35.)

38. Example 12 of the ’442 patent describes the results of a study designed to determine the binding capacities of α-, β-, and γ-iron oxy-hydroxides that were “stabilized” by “[s]accharose and starch in a Fe:saccharose:starch weight ratio of 1:1.5:1.5.” (JTX-0003 at 8:39-9:28.)

39. Example 13 of the ’442 patent describes the results of a study designed to determine the binding capacity of an adsorbent material made by adding 0.96 g of calcium acetate to 5 g of the material prepared in accordance with Example 1. (JTX-0003 at 9:30-53.)

40. Example 15 of the ’442 patent describes a study designed to determine the amount of saccharose that could be detected in the material prepared in accordance with Example 6 when suspended in water. (JTX-0003 at 9:54-64.)

41. Example 16 of the ’442 patent describes an analysis of the phosphate content in foodstuffs mixed with the adsorbent material of Example 1. (JTX-0003 at 9:64-10:34.) According to Dr. Chambliss, Example 16 is the only example of the ’442 patent in which a stabilized iron oxy-hydroxide of the alleged invention is administered with food. (Tr. 294:13-295:3.)

42. The materials described in Examples 1, 6, and 8 all demonstrated 100% inorganic phosphate binding capacity at pH 3.0. (JTX-0003 at 3:53-4:13, 5:23-43, 5:64-6:18.) According to Plaintiffs’ own documents, pH 3.0 “reflects the physiological conditions in the stomach when [the phosphate binder] is taken with food.” (DTX-0073.0031.) By comparison with Example 1, Example 7 exhibited significantly worse phosphate binding capacity at every pH, and Example 8 only performed better (by a mere 6%) at pH 5.5. (JTX-0003 at 3:53-4:13, 5:44-6:18.)

43. With respect to Example 7, Dr. Chambliss testified that he has not seen Amylopectin used as an excipient in a pharmaceutical product, and the compound is not mentioned as an excipient in the Handbook of Pharmaceutical Excipients. (Tr. 480:20-25.) With respect to Example 8, Dr. Chambliss testified that dextrin will result in a less palatable and flowable composition than Example 1. (Tr. 479:16-480:3.) In all of the Examples of the ’442 patent, the iron oxy-hydroxide must be stabilized so it does not deteriorate over time. (Tr. 294:9-12.) The addition of starch to saccharose (as in Example 1) would prevent most degradation of the active iron oxy-hydroxide over time. (Tr. 390:10-14.) The class of compounds disclosed in the ’442 patent is stabilized longer through the addition of starch in Example 1 than in any of the other Examples. (Tr. 391:16-19.)

44. According to Dr. Chambliss, the stabilization agents used in Example 1 (saccharose and starch) are commonly used to make both oral suspensions and chewable tablets, and Example 1 is the only Example that would be “read to go” for formulation without additional excipients. (Tr. 292:16-293:3.)

45. Dr. Williams conceded that all of the exemplary compositions in the ’442 patent have the same active moiety (iron oxy-hydroxide) and that any other constituents are excipients. (Tr. 705:10-706:13.)

B. Hergesell

46. Hergesell, titled “Stabilized Polynuclear Iron Hydroxide is an Efficient Oral Phosphate Binder in Uraemic Patients,” published in 1999. (JTX-0007.1.)

47. Hergesell reports the results of a clinical study conducted on 13 patients “to test the efficacy and tolerability of [a stabilized polynuclear iron hydroxide phosphate binder] in hyperphosphataemic patients with stable preterminal renal failure [and] to assess the effect of oral

administration of this compound on plasma and urinary Pi." (JTX-0007.1.)

48. Hergesell discloses that the composition used in the clinical study was provided by Dr. Geisser and Dr. Philipp of the Vifor Company. (JTX-0007.4.) Patients were administered "a constant dose of 3×2.5 g stabilized polynuclear iron hydroxide (courtesy Vifor Company, St. Gallen, Switzerland) provided as a powder in preweighed sachets. The material was suspended in water and ingested together with meals." (JTX-0007.2.) Only a small amount of water was needed to dissolve the product: "[t]he average volume of water consumed by dissolving the contents of the sachets was 75 ml per sachet (range 50–100 ml)." (JTX-0007.2.) Dr. Chambliss testified that such disclosures teach administration of the phosphate binder three times a day with meals. (Tr. 304:16-17.)

49. According to Dr. Chambliss, Hergesell taught a single sachet dosage form of 2.5 grams of stabilized polynuclear hydroxide powder given three times a day with meals, consistent with the '442 patent's teaching that the disclosed iron oxy-hydroxide compositions should be administered simultaneously with food. (Tr. 335:17-23, 336:2-7, 336:10, 343:23-25.) Further, Hergesell tested a sachet containing 500 mg iron—i.e., 800 mg iron oxy-hydroxide. (Tr. 343:22-344:15.)

50. According to Hergesell, "no side effects were noted" and "[t]he tolerability of the compound was excellent (this was confirmed by the investigators who also ingested the compound over the same period)." (JTX-0007.1, 3.)

51. Hergesell specifically directs the reader to reference [13] (the '356 application) for further "product information" concerning the "insoluble" polynuclear iron(III)-hydroxide administered in the study. (JTX-0007.3-4.) As discussed above, the '356 application is the German priority application to the '442 patent and contains the same disclosure.

52. Hergesell states that "stabilized polynuclear iron hydroxide [13], chemical formula $[FeO_{2/3}(OH)_{5/3}H_2O$ l/m $(C6H_{10}O_5)_m]_n$ appears to be a promising, new compound which has remarkable in vitro binding capacity for phosphate (Pi)." (JTX-0007.1.) According to Dr. Chambliss, the chemical formula is non-standard. (Tr. 402:4-403:2.) Dr. Harris, an expert witness for Plaintiffs that was not called at trial, reportedly agreed with Dr. Chambliss on this point. (Tr. 402:25-403:1.) For example, neither Dr. Chambliss nor Dr. Harris knew the meaning of the "l" or "l/m" in the chemical formula, and the formula contained clear errors. (Tr. 403:8-17.) Dr. Chambliss also testified that a POSA looking at the '442 patent would consult the Hergesell reference for clinical confirmation rather than information regarding the chemical formula. (Tr. 401:10-17.)

53. Dr. Chambliss credibly testified that the carbohydrate portion of the formula, if rewritten as $C_6H_{10}O_5$, would be consistent with starch (used in Example 1 in combination with saccharose), amylopectin (used in Example 7), and dextrin (used in Example 8). (Tr. 404:12-15-17, 406:22-407:2, 407:8-10.)

54. According to Dr. Chambliss, the chemical formula in Hergesell is incomplete. (Tr. 407:11-408:5.) Further, the chemical formula excludes Example 6 (using only saccharose, $C_{12}H_{22}O_{11}$) and Example 9 (using humic acid), as neither includes a carbohydrate having a chemical formula that matches $C_6H_{10}O_5$. (Tr. 409:12-21.)

55. With respect to the chemical formula provided in Hergesell, Plaintiffs can only rely on the trial testimony of Dr. Williams, an expert who did not challenge or address the undisputed errors in the formula and had based his opinions regarding the formula entirely on another expert witness, Dr. Harris, who was not called at trial. (Tr. 667:15-672:12).

56. Dr. Chambliss credibly testified that a POSA would consider Example 1 (iron oxy-

hydroxide stabilized by saccharose and starch) to be the lead formulation of the '442 patent. (Tr. 413:6-7, 396:13-18.) Dr. Chambliss provided several reasons for this, including that Example 1: (1) is predominant and is repeatedly used in or as the basis for other Examples; (2) is the only Example material specifically referred to as a "powder"; (3) is the only Example disclosing material that is ready to be administered as a dosage form without additional excipients; (4) is the only Example disclosing material that is co-incubated with calcium acetate in Example 13; (5) features the same composition (iron oxy-hydroxide mixed with saccharose and starch) that is specifically refer to as "stabilized" in the Examples section; (6) would be the most effective Example at preventing deterioration of the iron oxy-hydroxide over time; (7) discloses the only composition tested in the '442 patent for organic phosphate binding; (8) discloses the only composition that is mixed with foodstuffs (in Example 16); and (9) is superior to the other Examples with respect to flowability, taste, aging, and/or frequency of usage in art. (Tr. 292:11-15, 293:15-23, 294:9-295:3, 388:12-22, 397:7-13, 477:19-480:25, 387:13-23.)

57. Because Example 1 contains both saccharose *and* starch, a POSA would recognize it as having the best profile in terms of taste/palatability and processability/flowability and would be ready to go as a dosage form. (Tr. 284:11-285:2, 292:16-293:3, 461:17-462:1, 478:5-12.)

58. Dr. Chambliss also testified that, based on the testimony of Dr. Philipp and the understanding of a POSA, the iron oxy-hydroxide composition administered in the Hergesell study was Example 1 of the '442 patent. (Tr. 307:13-19, 308:7-14, 317:4-10.)

59. According to Dr. Chambliss, the Hergesell study tested and confirmed the iron release and absorption properties of PA21. (Tr. 317:11-14.) Specifically, Hergesell disclosed that the administered composition was insoluble, would have little iron release, and would not be absorbed in the human body in a clinically significant amount. (Tr. 347:23-348:3, 348:10-20,

319:24-320:9, 357:6-13.) Dr. Chambliss further testified that a POSA would understand how solubility and release correlate, since solubility puts a constraint on how much drug can be released. (Tr. 319:24-320:23.) In particular, solubility testing test results dictate what release test results could be. (*Id.*) If a drug is not soluble in a media, it will not release and dissolve in the media. (*Id.*)

60. Dr. Chambliss testified that the Hergesell study showed that after five hours of a solubility test, only 2.1 percent of the drug was present in the media. (*Id.*) This is consistent with the Court's construction for iron release. (*Id.*) In addition, Hergesell's iron solubility test was run for 2.5 times longer than the Court's construction requires and got a lower release than required by the Court. (Tr. 358:14-20.)

61. Hergesell indicates that after 5 hours at 37 degrees and at a pH of 3 the in vitro release/solubility of the administered dose was only 2.1. (JTX-0007.4; Tr. 356:17-23.) Specifically, Hergesell reported the results of "[i]ron solubility in vitro after 5 h" at 37°C at a concentration of 500 mg Fe/l in order to evaluate the total release from the dosage form that was administered in the study, with the results being "between 0% (at pH 8) and 2.1% (at pH 3)." (JTX-0007.4.) Dr. Chambliss credibly testified that this solubility testing indicates that the release rate of iron oxy-hydroxide, tested in accordance with the Court's claim construction, would have been below 2.5%. (Tr. 319:19-320:23, 432:12-19.) In particular, the fact that only 2.1 percent of the iron in Hergesell goes into the solution after five hours in a solubility test indicates that less that 2.5 percent of the iron is released in a dissolution test at two hours. (Tr. 319:19-320:23.) Given that the solubility test lasts for 5 hours, it does not matter whether the flask is shaken or stirred. (Tr. 434:8-18.) As explained by Dr. Chambliss, the iron solubility test used in Hergesell is consistent with the teachings of the '442 patent. (Tr. 358:21-359:4.)

62. According to Hergesell, the results of the clinical study showed "a consistent decrease of plasma-Pi and a reduction of urinary-Pi in all of the 13 hyperphosphatemic patients with stable preterminal renal failure" indicating that "a substantial amount of phosphate had been bound in the intestine," and calculated that "1 g of polynuclear iron hydroxide binds approximately 1.33 mmol phosphate in humans." (JTX-0007.3-4.) Hergesell concluded that the "[s]tabilized polynuclear iron hydroxide is a promising, efficaceous [sic] and well tolerated phosphate binder" and "an effective oral phosphate binder in patients with renal failure." (JTX-0007.1.) Further, Hergesell discloses that "[n]o significant change of serum iron and serum ferritin concentrations were noted." (JTX-0007.4, Tr. 346:5-13, 318:1-11.)

63. According to Dr. Chambliss, the in vivo iron absorption tests reported in Hergesell confirm that the administered iron oxy-hydroxide composition did not result in clinically significant absorption of iron oxy-hydroxide. (Tr. 317:11-318:17.) As Dr. Chambliss testified, a POSA would have understood Hergesell's results consistently to show no clinically significant change in serum iron and serum ferritin concentration or serum iron absorption. (Tr. 318:1-17.)

64. When seeking regulatory approval for Velphoro, Plaintiffs specifically relied on the iron absorption results reported in Hergesell. (Tr. 318:18-21.) For example, Plaintiffs cited Hergesell in support of the efficacy of the iron cage phosphate binder agents, as well as Plaintiffs' conclusion that significant absorption of iron is not expected. (Tr. 318:23-319:11; DTX-0083.0009.) In addition, Dr. Rastogi agreed that there was no clinically significant amount of iron absorbed in the Hergesell test. (Tr. 347:1-5.) Plaintiffs also indicated (including to the regulatory authorities) that, based on prior data and toxicological studies regarding PA21, absorption was not a concern. (Tr. 351:14-22; DTX-0047.0006; DTX-0083.0019.)

65. Hergesell reports that the administered iron oxy-hydroxide composition was shown

to work for treating hyperphosphatemia. (JTX-0007.1, 4.) Hergesell repeatedly indicated that the pharmaceutical composition was suitable for oral administration, explaining that:

- The composition was an "efficacious and well tolerated phosphate binder" (JTX-0007.1);
- The study was to "assess the effect of [its] oral administration" (JTX-0007.1);
- "The material was suspended in water and ingested together with meals" (JTX-0007.2);
- "The tolerability . . . was excellent" (JTX-0007.3);
- The tolerability "was confirmed by the investigators who also ingested the compound over the same period" (JTX-0007.3); and
- "[T]he above results are encouraging and suggest that stabilized polynuclear iron hydroxide is an effective oral phosphate binder in patients" (JTX-0007.4.).

66. According to Dr. Chambliss, the tolerability of the compound was excellent and confirmed by the Hergesell investigators. (Tr. 332:21-333:3, 334:11-22.)

67. Years after the publication of Hergesell, Plaintiffs conducted a subsequent study in which the material administered in Hergesell (PA21) was orally administered in the same manner, i.e., "as a powder for suspension . . . in 75 ml water," and Plaintiffs confirmed Hergesell's conclusion that oral administration of the powder suspended in water was an efficacious and well-tolerated phosphate binder with low iron uptake. (DTX-0062.0004-6.) Specifically, Plaintiffs' reported "Findings" are that the "oral PA21 administration"—as a powder suspended in water—to eight (8) "nondialysis patients with CKD Stage 3 or 4," eight (8) CKD patients requiring maintenance hemodialysis," and eight (8) "healthy subjects," was "an efficacious and well-tolerated phosphate binder." (DTX-0062.0004-6.) The article was authored by Plaintiffs' own

scientists, including one of the named inventors of the ’251 and ’442 patents, Dr. Erik Philipp. DTX-0062.0001.)

C. The ’079 Patent

68. The ’079 patent issued on November 13, 1990. (JTX-0005.1)

69. Among other things, the ’079 patent discloses that iron oxy-hydroxides have been shown to be effective phosphate binders with low absorption of iron compounds. (JTX-0005 at 2:14-30.) The compositions disclosed in the ’079 patent may be used to control “serum phosphate levels in patients suffering from hyperphosphatemia or patients predisposed to development of a hyperphosphatemic condition.” (JTX-0005 at 2:42-46.)

70. The ’079 patent disclosed that iron oxy-hydroxides “exhibit low solubility in physiological fluids, including gastric juices, thereby lessening the probability of side effects due to absorption of solubilized iron compounds” and that, “due to their low solubility, provide little risk of side effects” and “contribute little to the levels of soluble iron concentration.” (JTX-5 at 2:20-23, 3:10-11, 4:15-20.)

71. Oral dosages of the iron oxy-hydroxide compounds in the ’079 patent can range from about 50 to about 500 mg or more. (JTX-0005 at 3:52-55.) According to Dr. Chambliss, these disclosures predating the ’442 patent teach an individual dose of 500 milligrams or more in a single unitary solid dosage form. (Tr. 303:23-304:2.) Specifically, the ’079 patent discloses a therapeutic dosage of iron oxy-hydroxide for oral administration in a unitary solid dosage form of approximately 50 to 500 milligrams. (Tr. 304:4-11.) Further, claims 1 and 14 of the ’079 patent teach that an oral dosage form of about 500 milligrams of iron oxy-hydroxide can be sufficiently effective at binding ingested phosphate, and that using such a compound may prevent or alleviate hyperphosphatemia. (Tr. 337:11-338:2.) A person of ordinary skill in the art would thus understand

from the ’079 patent that they could make a dosage form that contained 500 or more milligrams of iron oxy-hydroxide and administer it as to a patient afflicted with hyperphosphatemia. (Tr. 337:11338:2.)

72. The ’079 patent further teaches that iron oxy-hydroxide compounds “can be formulated as a liquid or gel suspension, or in a unitary solid dosage form such as a compressed tablet or capsule” using methods and excipients that are “well known in the art.” (JTX-0005 at 3:36-44.)

73. Dr. Chambliss credibly testified that the ’079 patent reflects an understanding in the prior art that the low iron release and absorption characteristics of iron oxy-hydroxide were desirable. (Tr. 300:5-19.) The ’079 patent disclosed that iron oxy-hydroxides are insoluble in physiological fluids, such as in the GI tract, and have high adsorption capacity for phosphate due to their low solubility. (*Id.*) This insolubility also reduces the probability of side effects due to absorption of solubilized iron compounds. (*Id.*)

74. According to Dr. Chambliss, the ’079 patent indicates that iron oxy-hydroxides are inherently insoluble even when not stabilized, and one would not want to jeopardize that insolubility by using a stabilizer that increases solubility and iron release. (Tr. 394:4-21)

D. Lieberman

75. Lieberman is a pharmaceutical treatise on the development of tablet dosage forms that was published in 1980. (JTX-0008.3; Tr. 287:21-288:14, 370:7-15.)

76. According to Dr. Chambliss, Lieberman reflects the understanding in the prior art that, due to the large amounts of active ingredient required, the most common forms for phosphate binders were oral suspensions and chewable tablets. (Tr. 364:3-9.)

77. Lieberman discloses that “[p]harmaceutical tablets are often required or desired to

be in a chewable form." (JTX-0008.61.) Desired properties of a chewable tablet formulation include good compression, good powder flow, pleasant taste, and good mouth-feel. (JTX-0008.70; Tr. 373:3-11.) According to Lieberman, sucrose is commonly used in chewable tablet formulations. (JTX-0008.70, 72; Tr. 372:13-373:2.)

78. Lieberman states that "starches are the most common disintegrating agents (Table 2) in use today" and "probably the most commonly used binder in the past." (JTX-0008.13.)

79. According to Dr. Chambliss, Lieberman teaches how to make chewable tablets. (Tr. 372:13-17.) Lieberman did not teach away from chewable tablets. (Tr. 368:6-12.)

80. Lieberman discloses studies describing chewable tablet formulations with loading capacities of between 33% and 92% depending on the composition of the excipients and the compressibility of the active pharmaceutical ingredient. (JTX-0008.78.)

81. According to Dr. Chambliss, many of the examples used in Lieberman taught chewable tablets with phosphate binders. (Tr. 368:6-12.) In particular, Lieberman discloses a number of high load chewable formulations for antacids that bind phosphate. (Tr. 370:8-15.) For example, Lieberman discloses a chewable antacid formulation comprising 350 mg of aluminum hydroxide and 100 mg of calcium carbonate in a 1,200 mg tablet. (Tr. 370:20-371:2; JTX-0008.94.)

82. Chewable tablets having the ingredients disclosed in Table 6 of Lieberman were high load and typically included 500 mg or more of the active ingredient. (Tr. 371:6-23; JTX-0008.94.)

83. Lieberman discloses examples of chewable antacid tablet formulations including tablets commonly containing 150 to 400 mg of aluminum hydroxide and/or 200 to 700 mg of calcium carbonate. (JTX-0008.94.) Lieberman also discloses a chewable antacid tablet formulation

comprising 240.0 mg of Aluminum hydroxide, 60.0 mg of Magnesium hydroxide, and 60 mg of Magnesium carbonate for a total active ingredient weight of 360 mg in a tablet that weighs 486.9 mg (i.e., a 73.9% drug load). (JTX-0008.53.) According to Dr. Chambliss, sugar and starch are used in chewable antacid tablets to mask their unpleasant taste. (Tr. 372:7-12.)

84. Lieberman discloses that it is a reasonably safe assumption "that a chewable antacid tablet will contain 400 mg to 900 mg of active ingredient," and the tablet weight "may be as much as 600 to 1,500 mg." (JTX-0008.94; Tr. 371:24-372:6.)

E. The '465 Patent

85. The '465 patent, entitled "Pharmaceutical Formulation Comprising Lanthanum Compounds," issued on December 16, 2008. (JTX-0004.1.)

86. The '465 patent teaches that hyperphosphatemia is a problem that occurs in about 70% of patients with end stage renal disease. (JTX-0004 at 1:11-14.) The '465 patent discloses that lanthanum carbonate formulations have been used to treat hyperphosphatemia but there is a need for a chewable tablet formulation comprising lanthanum carbonate. (JTX-0004 at 1:26-43.)

87. The '465 patent teaches a chewable formulation for a lanthanum carbonate phosphate binder with a high drug load and acceptable size for a patient. (Tr. 297:21-298:12.) According to Dr. Chambliss, the advantage of the '465 patent is higher strength phosphate binding tablets that reduce overall pill burden, an important issue for patient compliance. (Tr. 287:21-298:8, 338:3-19.)

88. The '465 patent discloses that "[a] typical dosage for an adult may be, e.g., 750 mg-3000 mg daily. The dose can be divided and taken with each meal, for example 250-1000 mg, e.g., three times per day. Serum plasma levels can be monitored weekly until an optimal serum phosphate level is reached conventionally." (JTX-0004 at 6:65-7:2.) The '465 patent discloses that

the pharmaceutical formulations described therein may be formulated as a chewable tablet, a powder, or a sprinkle for oral administration. (JTX-0004 at 2:17-57.)

89. The ’465 patent discloses chewable lanthanum carbonate tablets comprising sucrose and starch as excipients, as well as chewable tablet formulations having up to 1,000 mg of lanthanum and 10-40% loading. (Tr. 295:23-296:13; JTX-0004 at 4:26-67.) Example 1 of the ’465 patent discloses compositions and processes used to make 250, 500, 750, and 1000 mg lanthanum carbonate chewable tablets. (JTX-0004 at 8:49-9:44.) Example 2 of the ’465 patent discloses dosages of chewable lanthanum carbonate tablets ranging from 225 to 2250 mg/day. (JTX-0004 at 9:45-10:16.) The ’465 patent also claims “a chewable tablet, comprising lanthanum carbonate in an amount form about 200 mg to about 1000 mg elemental lanthanum in the proportion of about 10 to about 40 wt% of the formulation,” as well as a chewable tablet comprising 45.8% lanthanum carbonate (by weight). (JTX-0004 at claim 1, claim 8; Tr. 338:3-22.)

VI. THE ASSERTED CLAIMS ARE OBVIOUS UNDER 35 U.S.C. § 103

90. Dr. Chambliss credibly testified that the asserted claims are all invalid as obvious in view of: (1) the ’442 patent alone; and (2) the ’442 patent in combination with Hergesell and the general knowledge of a POSA (as reflected in the ’079 patent, Lieberman, and/or the ’465 patent). (Tr. 287:21-288:14, 305:23-306:5.)

91. As a pharmaceutical formulator, a POSA would start the prior art analysis with the compositions of the ’442 patent. (Tr. 287:15-20, 288:21-289:2, 305:23-306:5.)

92. The Examples of the ’442 patent include five compositions prepared according to the alleged invention of the ’442 patent: (i) Example 1 (iron oxy-hydroxide, sucrose, and starch); (ii) Example 6 (iron oxy-hydroxide and sucrose); (iii) Example 7 (iron oxy-hydroxide and amylopectin); (iv) Example 8 (iron oxy-hydroxide and dextrin); and (v) Example 9 (iron oxy-

hydroxide and humic acid). (JTX-0003 at 3:30-10:35.)

93. A POSA would look to Hergesell, which refers the reader to the disclosures of the ’442 patent for “product information” concerning the effective phosphate binder administered in the study, for information regarding the clinical use and properties of the phosphate binders taught in the ’442 patent. (Tr. 305:23-306:22.) As Dr. Chambliss credibly testified, Hergesell and the ’442 patent are “very tightly tied together.” (Tr. 305:23-306:5.)

94. At trial, Plaintiffs did not contest that a POSA would have been motivated to combine the teachings of the ’442 patent and Hergesell.

95. At trial, Plaintiffs only contested whether the following limitations of the asserted claims would have been obvious: (1) “at least 500 mg” of iron-oxyhydroxide “per dosage form”; (2) the “essentially non-bioabsorbable” and “release rate” limitations of claims 29 and 30; (3) the “chewable tablet” limitation of claim 33; and (4) the “about 800 mg iron oxy-hydroxide per dosage form” limitation of claim 56.

96. Dr. Chambliss credibly testified that the ’442 patent taught or suggested that the sucroferric oxy-hydroxide powder described in Example 1 of the ’442 could be successfully formulated into dosage forms that—in addition to containing “at least 500 mg” of iron-oxyhydroxide “per dosage form” and otherwise meeting every limitation of independent claims 1 and 27—practice: (1) the “essentially non-bioabsorbable” and “release rate” limitations of claims 29 and 30; (2) the “chewable tablet” limitation of claim 33; and (3) the “about 800 mg iron oxy-hydroxide per dosage form” limitation of claim 56. (Tr. 340:14-18, 341:19-342:11, 343:11-17, 348:21-24, 368:13-369:21.)

97. Dr. Chambliss credibly testified that a POSA would have been motivated to combine the teachings of the ’442 patent and Hergesell with the general knowledge of POSA (as

reflected in the ’079 patent, the ’465 patent, and Lieberman) and would have had a reasonable expectation that the sucroferric oxy-hydroxide powder described in Example 1 of the ’442 could be successfully formulated into dosage forms that—in addition to containing “at least 500 mg” of iron-oxyhydroxide “per dosage form” and otherwise meeting every limitation of independent claims 1 and 27—practice: (1) the “essentially non-bioabsorbable” and “release rate” limitations of claims 29 and 30; (2) the “chewable tablet” limitation of claim 33; and (3) the “about 800 mg iron oxy-hydroxide per dosage form” limitation of claim 56. (Tr. 295:23-298:12, 303:23-304:24, 317:11-321:25, 328:3-21, 330:24-347:14, 356:17-359:11, 367:9-376:18.)

A. Unasserted Independent Claim 1

98. Asserted claims 29, 30, and 33 ultimately depend from unasserted claim 1, which recites:

> 1. A pharmaceutical composition comprising an effective phosphate-adsorbing amount of iron oxy-hydroxide in high loading of 10 to 80% (w/w) expressed in relation to the total weight of the pharmaceutical composition, and carbohydrates, said carbohydrates compromising saccharose and starch, in a form suitable for oral administration, wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg.

(JTX-0001 at claim 1.)

99. Dr. Chambliss credibly testified that claim 1 was obvious in view of the prior art. (Tr. 329:21-340:18.)

100. At trial, Plaintiffs only contested the obviousness of the limitation “wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg.”

1. A pharmaceutical composition comprising an effective phosphate-adsorbing amount of iron oxy-hydroxide in high loading of 10 to 80% (w/w) expressed in relation to the total weight of the pharmaceutical composition

101. At trial, Plaintiffs did not present any evidence or argument that the limitation “[a]

pharmaceutical composition comprising an effective phosphate-adsorbing amount of iron oxy-hydroxide in high loading of 10 to 80% (w/w) expressed in relation to the total weight of the pharmaceutical composition" would not have been obvious in view of the prior art.

102. Dr. Chambliss credibly testified that the limitation "[a] pharmaceutical composition comprising an effective phosphate-adsorbing amount of iron oxy-hydroxide in high loading of 10 to 80% (w/w) expressed in relation to the total weight of the pharmaceutical composition" would have been obvious in view of the '442 patent. (Tr. 329:21-331:6.)

103. The '442 patent teaches that the disclosed iron oxy-hydroxide phosphate binders are suitable for treating patients afflicted with hyperphosphatemia. (Tr. 297:21-299:4; JTX-0003 at 1:5-10.) The material described in the '442 patent can be formulated "as such" (i.e., without additional excipients) or together with customary inactive ingredients. (Tr. 290:5-291:6, 296:14-20; JTX-0003 at 3:15-18.)

104. Example 1 of the '442 patent discloses that the iron oxy-hydroxide is stabilized with 15 grams of sucrose and 15 grams of starch. (Tr. 295:16-19; JTX-0003 at 3:30-51.) The resulting powder of Example 1 has an iron content of 21.2%. (Tr. 292:2-10; JTX-0003 at 3:30-51.) Because the content of iron oxy-hydroxide is approximately 1.6 times the iron content (Uncontested Facts at ¶ 32), the sucroferric oxy-hydroxide disclosed in Example 1 has an iron oxy-hydroxide content of 33.92%, which is within the claimed range. (Tr. 295:4-15, 329:25-330:8.) the compositions described in Examples 1, 6, 7, 8, and 9 all have the same high loading. (Tr. 330:4-8; JTX-0003 at 3:30-10:34.)

105. The '442 patent teaches that an effective daily dose of the stabilized phosphate binders is approximately 1.5 grams of iron, which is 500 mg of iron given three times a day with meals. (Tr. 301:7-24; JTX-0003 at 3:19-21.) Because the content of iron oxy-hydroxide is

approximately 1.6 times the iron content (Uncontested Facts at ¶ 32), each dosage form will preferably contain 800 mg of iron oxy-hydroxide, an effective phosphate adsorbing amount. (Tr. 330:9-18.)

106. According to the ’251 patent, the ’442 patent describes an effective phosphate adsorber that had been shown in Hergesell to be an efficient for treating hyperphosphatemia. (Tr. 330:24-331:6; JTX-0001 at 1:27-37.)

2. carbohydrates, said carbohydrates comprising saccharose and starch

107. Plaintiffs do not contest that the ’442 patent discloses “carbohydrates, said carbohydrates compromising [sic] saccharose and starch.” (Uncontested Facts at ¶ 27.)

108. At trial, Plaintiffs did not present any evidence or argument that the limitation “carbohydrates, said carbohydrates comprising saccharose and starch” would not have been obvious in view of the prior art.

109. Dr. Chambliss credibly testified that the limitation “carbohydrates, said carbohydrates comprising saccharose and starch” would have been obvious in view of the ’442 patent. (Tr. 331:7-21.)

110. The ’442 patent, and specifically Example 1, teaches iron oxy-hydroxide that is stabilized with saccharose and starch. (Tr. 295:16-19, 331:7-16; JTX-0003 at 1:56-65, 2:42-47, 3:30-51.) Further, the use of saccharose and starch in pharmaceutical compositions was generally known in the art. (Tr. 331:17-21.)

3. in a form suitable for oral administration

111. At trial, Plaintiffs did not present any evidence or argument that the limitation “in a form suitable for oral administration” would not have been obvious in view of the prior art.

112. Dr. Chambliss credibly testified that the limitation “in a form suitable for oral

administration" would have been obvious in view of the '442 patent and/or the prior art combination. (Tr. 331:22-333:3.)

a. The '442 Patent

113. The '442 patent teaches that the disclosed iron oxy-hydroxide phosphate binders are particularly suitable for oral administration. (Tr. 298:21-299:4, 331:22-332:2; JTX-0003 at 1:5-10, 3:9-10.) The specification of the '442 patent also lists several suitable dosage forms for oral administration, including powders, granules, and tablets, among others. (Tr. 290:5-291:6, 297:3-9; JTX-0003 at 3:15-18.)

114. All of the dosage forms disclosed in the '442 patent were well-known and commonly used for the oral administration of phosphate binders. (Tr. 297:10-14.) Dr. Chambliss was involved in making all of the dosage forms during the 1980s and 1990s. (*Id.*) For administration to adults, oral suspensions and chewable tablets were the preferred dosage forms. (Tr. 297:15-20.)

b. The Prior Art Combination

115. As discussed above, the "form suitable for oral administration" limitation was disclosed and suggested by the '442 patent.

116. Hergesell teaches that the administered phosphate binder was suitable for oral administration. (Tr. 334:11-335:3; JTX-0007.1-4.) The composition was provided as a powder in a sachet and was ingested with water after meals. (Tr. 332:3-20; JTX-0007.2) Hergesell discloses that the tolerability of the phosphate binder—which the investigators tried for themselves—was excellent, that the composition was promising and efficacious, and that the encouraging results suggested that stabilized polynuclear iron hydroxide is an effective oral phosphate binder in patients. (Tr. 332:3-333:3, 334:11-335:3; JTX-0007.1, 3-4)

4. wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg

117. Dr. Chambliss credibly testified that the limitation "wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg" would have been obvious in view of the '442 patent and/or the prior art combination. (Tr. 335:4-340:12.)

a. The '442 Patent

118. Consistent with the general knowledge in the field at the time of the invention, a POSA would have been motivated to include at least 500 mg or more in a single dosage form, in the manner identified in the '442 patent, in order to reduce pill burden. (Tr. 295:23-298:12, 303:23-304:24, 456:24-462:14, 657:20-658:6, 713:10-714:8; JTX-0003 at 3:36-55; PTX-0544.1; DTX-0120.; JTX-0007.2; JTX-0004 at 6:56-59, claim 1.)

119. POSA would have had a reasonable expectation of success of being able to formulate a single dosage form of at least 500 mg using the "powder" of Example 1, especially given the '442 patent's affirmative statement that they "can" be formulated "as such or together with customary drug additives, such as customary carriers or auxiliary materials," including "as granules, tablets, dragees or contained in sachets." (Tr. 335:17-336:20, 704:13-25, 296:16-298:18, 332:3-20; JTX-0003 at 3:9-20.)

120. The '442 patent teaches that the preferred daily dose of the stabilized phosphate binders is approximately 1.5 grams of iron. (Tr. 301:7-24, 335:4-16; JTX-0003 at 3:19-21.) A POSA would know that the phosphate binders would be administered three times per day with meals. (Tr. 301:15-24, 290:5-291:15; JTX-0003 at 3:18-25, claim 12.) Thus, a POSA would recognize that the '442 patent's preferred amount of iron per dosage form is 500 mg (i.e., one-third of the 1.5 g preferred daily dose). (Tr. 335:4-16.) Because the content of iron oxy-hydroxide is approximately 1.6 times the iron content (Uncontested Facts at ¶ 32), each dosage form would

preferably contain 800 mg of iron oxy-hydroxide. (Tr. 330:9-18, 335:4-16.)

121. At trial, Plaintiffs agreed that a POSA would understand the ’442 patent’s teaching of a “preferred” daily dose of 1.5 g of iron to equal an individual dose of 500 mg of iron (i.e., 800 mg of iron oxy-hydroxide) that would be administered 3-times per day with meals. (Tr. 711:21-712:11; JTX-3 at 3:19-21; PTX-217.1.). Dr. Williams, Plaintiffs’ formulation expert, testified that the state of the art recognized that at least 500 mg of oxy-iron compounds was necessary to achieve an effective level of phosphate adsorption. (Tr. 706:17-21). Dr. Williams also testified that a POSA would understand that the iron oxy-hydroxide compositions of the ’442 patent would be taken with food, but he would need to consult a clinician to determine whether that would mean three times per day. (Tr. 711:21-712:23.) Dr. Rastogi, Plaintiffs’ clinical expert, testified that “the assumption is that most of the people have three meals . . . [t]hey take three meals a day.” (Tr. 546:12-17.)

122. It was within the general knowledge of a POSA that phosphate binders are commonly administered with meals three times per day. Renvela (sevelamer carbonate) is a phosphate binder indicated for the control of serum phosphorous in patients with chronic kidney disease on dialysis. (Tr. 713:6-15; DTX-0120.0001.) Renvela was initially approved by FDA in 2000. (DTX-120.0001.) Renvela is available as 800 mg tablets and as a powder in 0.8 g and 2.4 g packets, which are similar to sachets. (Tr. 713:16-714:3; DTX-120.001.) Renvela’s starting dose is “0.8 or 1.6 grams to be administered orally three times per day with meals.” (Tr. 714:4-8; DTX-120.0001.) Similarly, Renagel (sevelamer carbonate) tablets were to be taken “three times per day with meals” (PTX-0214.1), Phoslyra (calcium acetate) was an oral solution to be taken “with each meal” (PTX-0211.1), and Fosrenol (lanthanum carbonate) chewable tablets had an initial total daily dose of 1500 mg, which patients were instructed to “[d]ivide” and “[t]ake . . . with or immediately after meals.” (PTX-0544.1.)

123. It is common sense, and best practice, in the pharmaceutical industry to put the amount of active ingredient to be administered with a meal into a single dosage form (e.g., a single tablet). (Tr. 458:4-6.) Pharmaceutical formulators are motivated to maximize the amount of active in a tablet in order to minimize the number of tablets needed. (Tr. 458:25-459:7.)

124. At trial, Plaintiffs did not present any evidence that a POSA would choose to formulate the compositions of the ’442 patent such that the 500 mg of iron to be administered with each meal would be provided in multiple dosage forms (e.g., in two 250 mg tablets) rather than a single dosage form.

b. The Prior Art Combination

125. As discussed above, the limitation of “at least 500 mg” of iron oxy-hydroxide in a single dosage form was disclosed and suggested by the ’442 patent.

126. Hergesell confirmed the general practice of administering a phosphate binder 3 times per day “with meals,” as well as doing so with a high load of iron oxy-hydroxide in a single dosage form (i.e., a sachet powder packet) containing approximately 800 mg of iron oxy-hydroxide. (Tr. 301:8-302:6, 335:17-23; JTX-7.2.)

127. Hergesell taught and suggested a dosage form containing 500 mg of iron (i.e., 800 mg of iron oxy-hydroxide) based on the reported solubility testing of 500 mg of iron, which a POSA would have understood as a test of the administered dosage. (Tr. 335:17-337:10; JTX-0007.4.) A POSA would also understand the Hergesell powder to contain approximately 21.2% iron (i.e., about 848 mg of iron oxy-hydroxide in a 2.5 g sachet), as that iron percentage was contained in every example of the ’442 patent. (Tr. 329:25-330:8; JTX-0003 at 3:30-10:34.)

128. Prior to the ’442 patent, the ’079 patent disclosed and suggested a “unitary solid dosage form such as a compressed tablet” containing “500 mg or more” of iron oxy-hydroxide in “each oral dose.” (Tr. 303:23-304:11; JTX-0005 at 3:36-55.) At trial, Dr. Williams conceded that

the “state of the art” taught as much. (Tr. 706:17-21.)

129. The ’079 patent’s disclosure of a high load single dosage form “such as a compressed tablet” would have further suggested a chewable tablet form to a POSA. (JTX-0005.3, 3:36-55.)

130. Hergesell teaches the administration of a phosphate binder—which was described in the ’442 patent—with meals three times per day. (Tr. 304:12-305:14; JTX-0007.2.) The purpose of the Hergesell study was to test efficacy of the composition when orally administered to patients. (Tr. 305:1-14.) Hergesell teaches that 2.5 g of the powder, provided in a sachet (i.e., a single dosage form), was administered three times per day. (Tr. 335:17-23, 336:8-10; JTX-0007.2.) Patients would open the sachets, mix the powder with about a third of a glass of water, and ingest the oral suspension. (Tr. 305:1-14; JTX-0007.2.)

131. All of the Examples compositions prepared according to the invention of the ’442 patent comprised 21.2% iron. (Tr. 336:21-24, 329:25-330:8; JTX-0003 at 3:30-10:34) Thus, a POSA understand that the powder administered in Hergesell comprised 21.2% iron. (Tr. 336:21-24.)

132. Hergesell reports solubility testing on a sample of the powder comprising 500 mg of iron. (Tr. 336:11-20; JTX-0007.4.) A POSA would understand that the solubility testing would have been performed on a single dosage unit (i.e., the amount of powdered contained in a single sachet). (Tr. 336:11-20, 336:25-337:10.) Thus, a POSA would understand that each sachet of powder administered in the Hergesell study comprised 500 mg of iron, which corresponds to 800 mg of iron oxyhydroxide. (Tr. 336:11-20, 336:25-337:10, 343:22-344:10.)

133. As reflected in the ’079 patent, it would have been within the general knowledge of a POSA they could develop a dosage form comprising 500 mg or more of iron oxy-hydroxide.

(Tr. 337:11-339:3.) The ’079 patent teaches orally administering a solid dosage form (e.g., a single compressed tablet or capsule) containing about 50 mg to about 500 mg or more of iron oxyhydroxide compound to a patient afflicted with hyperphosphatemia. (Tr. 337:11-23, 303:23-304:11; JTX-0005 at 3:36-55.) Claims 1 and 14 of the ’079 patent teach an amount effective to bind sufficient ingested phosphate to prevent or alleviate hyperphosphatemia using an oral dosage form of about 500 milligrams of iron oxy-hydroxide. (Tr. 337:11-338:2; JTX-0005 at claims 1 and 14.)

134. As reflected in the ’465 patent, it would have been within the general knowledge of a POSA that a phosphate binders have could be developed as a high load chewable tablet in order to reduce the number of tablets that a person has to swallow or chew. (Tr. 337:11-339:3; JTX-0004 at 3:11-15, 9:21-44, 13:20-22.) The ’465 patent teaches chewable phosphate binders comprising a high load of lanthanum carbonate. (Tr. 297:21-298:12; JTX-0004 at 3:11-15, 9:21-44, 13:20-22.) The chewable tablets contain up to 1,000 mg of lanthanum, an active ingredient load of 10-40%, and common excipients for making a chewable tablet (including starch and sucrose). (Tr. 339:10-18, 295:23-296:13, 297:21-298:12; JTX-0004 at 9:21-44, 13:20-22, claim 1.) Claim 1 of the ’465 patent discloses a chewable lanthanum carbonate tablet from about 200 milligrams to 1,000 milligrams. (Tr. 338:3-8; JTX-0004 at claim 1.) The ’465 patent teaches that the advantage of higher strength tablets is reduced overall pill burden, which is an important issue affecting patient compliance. (Tr. 297:21-298:12; JTX-0004 at 13:20-22.)

135. The ’465 patent teaches a chewable tablet that weighs 4,168 mg, and Dr. Chambliss has made chewable tablets weighing five grams (Tr. 339:19-340:12; JTX-0004 at 9:21-44.)

B. Unasserted Independent Claim 27

136. Asserted claim 56 ultimately depends from unasserted claim 27, which recites:

> 27. A method for treating hyperphosphatemia, comprising the steps of orally administering a pharmaceutical composition comprising an effective phosphate-adsorbing amount of iron oxy-hydroxide in high loading of 10 to 80% (w/w) expressed in relation to the total weight of the pharmaceutical composition, and carbohydrates, said carbohydrates comprising saccharose and starch, in a form suitable for oral administration, wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg, to a patient in need thereof.

(JTX-0001 at claim 27.)

137. The only difference between claims 1 and 27 of the ’251 patent is that claim 27 recites a method of treating hyperphosphatemia. (Tr. 340:20-341:4.) All of the prior art disclosures pertaining to claim 1 apply equally to the identical limitations in claim 27. (Tr. 341:12-342:21.)

138. Dr. Chambliss credibly testified that claim 27 was obvious was obvious in view of the prior art. (*Id.*)

139. At trial, Plaintiffs only contested the obviousness of the limitation “wherein the amount of iron oxy-hydroxide per dosage form is at least 500 mg.” (Tr. 689:12-17.)

1. A method of treating hyperphosphatemia, comprising the steps of orally administering . . . to a patient in need thereof

140. At trial, Plaintiffs did not present any evidence or argument that the limitation “[a] method of treating hyperphosphatemia, comprising the steps of orally administering . . . to a patient in need thereof” would not have been obvious in view of the ’442 patent and/or the prior art combination.

141. Dr. Chambliss credibly testified that the limitation “[a] method of treating hyperphosphatemia, comprising the steps of orally administering . . . to a patient in need thereof” would have been obvious in view of the ’442 patent. (Tr. 341:19-342:11.)

a. The ’442 Patent

142. The ’442 patent teaches that the disclosed iron oxy-hydroxide phosphate binders were particularly suitable for oral application to treat hyperphosphatemia. (Tr. 341:19-342:6; JTX-

0003 at 1:5-10.)

b. The Prior Art Combination

143. As discussed above, the "[a] method of treating hyperphosphatemia, comprising the steps of orally administering . . . to a patient in need thereof" limitation was disclosed and suggested by the '442 patent.

144. Plaintiffs do not contest that the administration of the iron oxy-hydroxide material in Hergesell satisfied the limitation "[a] method for treating hyperphosphatemia, comprising the steps of." (Uncontested Facts at ¶ 29.)

145. Hergesell reported the use of an orally administered phosphate binder—which was described in the '442 patent—to treat hyperphosphatemia. (Tr. 341:19-342:6; JTX-0007.1, 4.)

C. Asserted Dependent Claim 29

146. Asserted claim 29 recites:

> 29. The composition according to claim 1, wherein the iron oxy-hydroxide is essentially non-bioabsorbable.

(JTX-0001 at claim 29.)

1. wherein the iron oxy-hydroxide is essentially non-bioabsorbable

147. Dr. Chambliss credibly testified that the limitation "wherein the iron oxy-hydroxide is essentially non-bioabsorbable" would have been obvious in view of the '442 patent and/or the prior art combination. (Tr. 345:8-354:23.)

148. At trial, none of Plaintiffs' experts contested the prima facie invalidity of the limitation "wherein the iron oxy-hydroxide is essentially non-bioabsorbable."

a. The '442 Patent

149. The '442 patent suggested the "essentially non-bioabsorbable" limitation and that a POSA would have had a reasonable expectation of achieving it. (Tr. 344:19-363:10.)

150. The ’442 patent teaches that the iron oxy-hydroxides prepared according to the invention are insoluble and release little iron. (Tr. 345:8-19, 356:5-16; JTX-0003 at 2:58-62.) A POSA would also understand that these properties apply to the composition described in Example 1 of the ’442 patent. (Tr. 299:24-300:4.) It was also generally known at the time of the ’442 patent that the adsorption materials were insoluble and released little iron. (Tr. 299:5-11.) A POSA would expect that, if there is little iron release, would be little iron oxy-hydroxide available for absorption and iron oxy-hydroxide would not be absorbed by the human body in a clinically significant amount. (Tr. 345:8-19, 347:15-22, 356:5-16.) Similarly, POSA would know that material that is insoluble in water will not be released from the dosage form and thus will not be available to be absorbed. (Tr. 299:15-19.) A POSA would understand that a composition that is insoluble and releases little iron will be essentially non-bioabsorbable. (Tr. 289:17-290:4, 347:15-22.) Thus, the disclosures of the ’442 patent would provide a reasonable expectation of success in meeting the “essentially non-bioabsorbable” limitation. (Tr. 289:17-290:4, 299:5-300:24, 317:4-321:2.)

151. The fact that iron oxy-hydroxides did not raise iron absorption concern due to their insolubility was within the general knowledge of a POSA. (Tr. 300:5-19; JTX-0003 at 2:1-8, 2:14-23, 4:15-19.)

152. At trial, Plaintiffs’ experts did not address the teaching in the ’442 patent that the iron oxy-hydroxides prepared according to the invention are insoluble and release little iron. Plaintiffs’ clinical expert, Dr. Rastogi, testified in the infringement context that a composition meets the “essentially non-bioabsorbable” limitation if “the active moiety of sucroferric oxyhydroxide is insoluble or practically insoluble, and therefore, not absorbed. (Tr. 102:11-19.)

b. The Prior Art Combination

153. As discussed above, the “essentially non-bioabsorbable” limitation was disclosed and suggested by the ’442 patent.

154. The ’079 patent disclosed that iron oxy-hydroxides “exhibit low solubility in physiological fluids, including gastric juices, thereby lessening the probability of side effects due to absorption of solubilized iron compounds,” and that “due to their low solubility, provide little risk of side effects,” and thus “contribute little to the levels of soluble iron concentration.” (JTX-0005 at 2:20-23, 3:10-11, 4:15-20.) The expectation of a POSA, therefore, would have been that the iron oxyhydroxide of Example 1 would exhibit low iron absorption and release/solubility. (Tr. 300:5-19, 354:14-18.)

155. Hergesell’s *in vivo* test results showed the administered iron oxy-hydroxide from the ’442 patent was not absorbed by patients in a clinically significant amount, and also independently provided a POSA with a reasonable expectation that the “insoluble” compositions of Hergesell and the ’442 patent were “essentially non-bioabsorbable.” (Tr. 111:2-17, 128:11-25, 317:11-318:17, 347:6-350:16; JTX-0007.4; JTX-0003 at 2:58-62.)

156. Plaintiffs’ FDA documents confirm that they interpreted the Hergesell teachings the same way, i.e., as showing that “[clinically] [s]ignificant absorption of iron is not expected.” (Tr. 319:12-18; DTX-83.9; DTX-67.126, 179; DTX-77.91.)

157. Hergesell confirmed that “insoluble” phosphate binders of the ’442 patent would not result in a clinically significant amount of iron oxy-hydroxide absorption. (Tr. 317:11-14, 348:10-20.; JTX-0007.1, 4.) Hergesell describes an *in vivo* study for iron absorption and notes that there was no significant change of serum ferritin levels during the study. (Tr. 317:15-318:11, 346:5-13; JTX-0007.4.) The serum iron level did not increase in human patients when they administered the phosphate binder for 28 days. (Tr. 348:4-9; JTX-0007.4.)

158. Plaintiffs relied on the iron absorption results from Hergesell when seeking FDA approval for Velphoro. (Tr. 318:18-21.) Plaintiffs’ investigator’s brochure (DTX-0083) cited

Hergesell for the efficacy of the iron cage phosphate binder agents as demonstrated in a four-week in vivo study in uremic patients. (Tr. 318:23-319:6; DTX-83.9) According to Vifor, Hergesell concluded that significant absorption of iron is not expected. (Tr. 318:23-319:18; DTX-83.9; DTX-67.126, 179; DTX-77.91)

159. Plaintiffs' clinical expert, Dr. Rastogi, testified at his deposition that there was no clinically significant amount of iron absorbed in the Hergesell study. (Tr. 346:23-347:5.)

160. Hergesell describes the administered compound as "insoluble" polynuclear iron oxy-hydroxide. (Tr. 356:17-19; JTX-0007.2) Hergesell tested the iron solubility of the phosphate binder *in vitro*, which demonstrated that the composition was insoluble and would have little iron release. (Tr. 319:24-320:9; JTX-0007.4.) After five hours of the solubility test, only 2.1 percent of the iron was present in the media. (Tr. 320:10-20, 356:17-23; JTX-0007.4)

161. As reflected in the '079 patent, it would have been within the general knowledge of a POSA that the iron oxy-hydroxides disclosed in the '442 patent did not present iron absorption concerns. (Tr. 300:5-19; JTX-0005 at 1:1-5, 2:1-8, 2:14-23.) The '079 patent teaches that iron oxy-hydroxide exhibits low solubility in physiological fluids, lessening the probability of side effects due to absorption of solubilized iron compounds. (Tr. 348:25-349:11; JTX-0005 at 1:1-5, 2:1-8, 2:14-23.) The '079 patent teaches that iron oxy-hydroxide compounds have low water solubility over a wide pH range, as found in the gastrointestinal tract, and contribute little to the concentration of soluble iron in the digestive tract. (Tr. 350:8-13; JTX-0005 at 4:15-19.) This information was available before the effective date of the '442 patent. (Tr. 350:14-16.)

162. At trial, Plaintiffs' experts did not address the teachings in Hergesell and the '079 patent that iron oxy-hydroxides prepared according to the '442 patent are insoluble and release little iron.

D. Asserted Dependent Claim 30

163. Asserted claim 30 recites:

> 30. The composition according to claim 1, having an iron release rate of below 2.5% w/w.

(JTX-0001 at claim 30.)

1. an iron release rate of below 2.5% w/w

164. Dr. Chambliss credibly testified that the limitation "an iron release rate of below 2.5% w/w" would have been obvious in view of the '442 patent and/or the prior art combination. (Tr. 356:24-360:14, 361:14-363:10.)

165. At trial, none of Plaintiffs' experts contested the prima facie invalidity of the limitation "an iron release rate of below 2.5% w/w."

a. The '442 Patent

166. The '442 patent teaches that the iron oxy-hydroxides prepared according to the invention are insoluble and release little iron. (Tr. 345:8-19, 356:5-16; JTX-0003 at 2:58-62.) A POSA would also understand that these properties apply to the composition described in Example 1 of the '442 patent. (Tr. 299:24-300:4.) It was also generally known at the time of the '442 patent that the adsorption materials were insoluble and released little iron. (Tr. 299:5-11.) A POSA would know that material that is insoluble in water will not be released from the dosage form. (Tr. 299:12-19.)

167. A POSA would have been motivated to minimize iron release such that the "little release of iron" for the compositions disclosed in the '442 patent would have a rate below 2.5%. (Tr. 356:24-357:5; JTX-0003 at 2:58-62.)

168. At trial, Plaintiffs' experts did not address the teaching in the '442 patent that the iron oxy-hydroxides prepared according to the invention are insoluble and release little iron

169. At trial, Plaintiffs did not provide evidence of any criticality or unexpected results

associated with the claimed iron release rate of "below 2.5%." Plaintiffs clinical expert, Dr. Rastogi, admitted that his unexpected results analysis did not use "the exact number of 2.5 percent" but instead used different language—"very little, if any, iron is released"—that matches the teachings of the '442 patent. (Tr. 521:20-25, 525:24-526:9.) Such testimony reinforces that the teachings of the '442 patent are invalidating. (Tr. 356:24-357:5.)

b. The Prior Art Combination

170. As discussed above, the "release rate" limitation was disclosed and suggested by the '442 patent.

171. Hergesell's reported *in vitro* iron solubility result of 2.1% after 5 hours—taken with the '442 patent's teaching that all the disclosed compositions are insoluble and release little iron—would have taught or suggested that an iron "release rate below 2.5%" was achieved by the administered composition, and would have provided an expectation that it would be achieved by the compositions of the '442 patent, including Example 1. (Tr. 319:19-321:2, 356:5-359:11, 432:12-437:15, 477:19-25; JTX-0007.4.) A POSA would have understood that the iron solubility testing (run at the same temperature and pH of 3) in Hergesell was more rigorous than the test required by the Court's claim construction and, thus, based on the iron release of 2.1% after 5 hours in Hergesell, a POSA would have had an expectation of achieving Claim 30's release rate of below 2.5%. (Tr. 319:19-321:2, 356:5-359:11.)

172. Hergesell tested the iron solubility of the administered phosphate binder *in vitro*, which demonstrated that the composition—which was described in the '442 patent"—was insoluble and would have little iron release. (Tr. 317:11-14, 319:24-320:23, 336:25-337:10; JTX-0007.4.) The results of the iron solubility test in Hergesell are consistent with the teaching in the '442 patent that the disclosed phosphate binders are "insoluble." (Tr. 358:21-359:4.)

173. A POSA would understand that the iron release rate is limited based on the

solubility of the drug. (Tr. 320:10-20, 357:15-358:13.) If a drug is not soluble in a media, it will not release and dissolve in the media. (Tr. 320:10-20.) The solubility test dictates what the release test results would be. (Tr. 320:21-23.)

174. After five hours of the solubility test, only 2.1 percent of the iron was present in the media. (Tr. 320:16-20; JTX-0007.4.) The data in Hergesell would inform a person of skill in the art that, if they ran the European Pharmacopeia test method, the iron release rate would be less than 2.5 percent. (Tr. 432:12-19.) After five hours, the result would be the same regardless of how the sample was stirred or shaken. (Tr. 434:8-18.)

175. The solubility testing in Hergesell was performed at the same temperature and pH required by the Court's construction, was run for 2.5 times longer than the Court's construction, and resulted in lower release than required by the Court's construction (Tr. 320:10-23, 357:6-359:4; JTX-0007.4.)

176. A POSA would understand that if only 2.1 percent of the iron went into solution after five hours of the solubility test, less than 2.5% of the iron would be released in a dissolution test at two hours. (Tr. 319:19-320:23; JTX-0007.4.)

177. At trial, Plaintiffs' experts did not address the teachings in Hergesell that iron oxy-hydroxides prepared according to the '442 patent are insoluble and release little iron.

E. Asserted Dependent Claim 33

178. Asserted claim 33 depends from unasserted claim 33, which recites:

> 32. The composition according to claim 1, which is a dosage form capable of disintegration in the oral cavity.

(JTX-0001 at claim 32.)

179. Asserted claim 33 recites:

> The composition according to claim 32, wherein dosage form is selected from

chewable tablets.

(JTX-0001 at claim 33.)

1. a dosage form capable of disintegration in the oral cavity

180. At trial, Plaintiffs did not present any evidence or argument that the limitation "a dosage form capable of disintegration in the oral cavity" would not have been obvious in view of the prior art.

181. Dr. Chambliss credibly testified that the limitation "a dosage form capable of disintegration in the oral cavity" would have been obvious in view of the '442 patent. (Tr. 363:11-365:1.)

182. The '442 patent teaches that the disclosed iron oxy-hydroxide phosphate binders could be formulated "as such" (i.e., without additional excipients) as tablets and powders for oral administration, which would be capable of disintegrating in the oral cavity. (Tr. 363:18-364:2; JTX-0003 at 3:9-19.)

183. The '251 patent specifically acknowledges that tablets, powders, and other oral dosage forms disclosed in the '442 patent (e.g., granules) are capable of disintegrating in the oral cavity. (Tr. 364:13-23; JTX-0001 at 7:44-57.)

2. wherein dosage form is selected from chewable tablets

184. Dr. Chambliss credibly testified that the limitation "wherein dosage form is selected from chewable tablets" would have been obvious in view of the '442 patent. (Tr. 365:15-366:8.)

a. The '442 Patent

185. The '442 patent teaches that the disclosed iron oxy-hydroxide phosphate binders can be formulated as tablets with customary additives. (Tr. 366:17-367:4; JTX-0003 at 3:9-19.)

186. Example 1 of the '442 patent teaches a powder that can be used in an oral

suspension or compressed into a chewable tablet. (Tr. 367:5-9; JTX-0003 at 3:9-19, 3:30-51.)

187. Example 1 of the '442 patent contains a large amount starch and sucrose, which are two ingredients used in chewable tablets. (Tr. 369:1-21; JTX-0003 at 3:9-19, 3:30-51.) A person of ordinary skill in the art would understand that they could compress the powder into a tablet with or without additional inactive ingredients, or add other inactive ingredients and compress it into a tablet. (*Id.*)

188. Example 16 of the '442 patent teaches a chewable tablet, made from the composition described in Example 1, for administration to rats. (Tr. 386:18-387:4, 387:8-14, 387:20-388:8; JTX-0003 at 9:64-10:34.)

189. The '442 patent teaches that the preferred daily dose for the disclosed phosphate binders is 1.5 grams of iron per day, with each dosage form preferable containing 800 mg of iron oxy-hydroxide. (Tr. 366:17-367:4; JTX-0003 at 3:19-21.) Given this high load, as well as the understanding that a chewable tablet can be significantly larger than a swallowable tablet, a POSA would consider formulating the phosphate binder as a chewable tablet. (Tr. 325:4-326:3, 366:17-367:25.) A POSA would understand that a chewable tablet would require significantly less water intake, which must be limited for patients suffering from hyperphosphatemia. (Tr. 366:1-8.) A person of ordinary skill in the art knows how to formulate a chewable tablet. (Tr. 471:5-8.) Chewable tablets were already one of the primary dosage forms for phosphate binders when Dr. Chambliss began developing phosphate binders in the 1980s. (Tr. 365:7-14.) That a patient might mistakenly swallow a chewable tablet instead of chewing it would not dissuade a formulator from making a chewable tablet. (Tr. 471:16-472:16.)

190. At trial, Dr. Williams admitted that he had no prior experience with iron oxy-hydroxides and did not have any evidence that a POSA would have difficulties formulating a

chewable tablet due to issues with the taste or flowability of the powder described in Example 1 of the ’442 patent. (Tr. 715:14-719:22.)

191. At trial, Dr. Williams admitted that the asserted claims do not recite specific limitations regarding taste or flowability. (Tr. 701:6-20.)

192. Plaintiffs’ regulatory documents indicate that starch was added in order to improve flowability of the powder. (PTX-323.12; DTX-82.13; DTX-67.24; DTX-65.) Dr. Williams admitted that Plaintiffs added starch in order to the improve flowability of the powder. (Tr. 717:13-21.)

193. Plaintiffs’ regulatory documents indicate that sucroferric oxy-hydroxide tastes slightly sweet. (PTX-323.13.) Dr. Williams admitted that he did not consider regulatory documents from Plaintiffs which indicate that sucroferric oxy-hydroxide powder does not suffer from taste issues. (Tr. 717:22-718:25.)

194. At trial, Dr. Williams cited prior art indicating that sucrose was one of the most well-known chewable tablet excipients for addressing taste and palatability issues. (DTX-39.12-13; DTX-1006.26, 29-30.)

195. At trial, Dr. Williams cited prior art indicating that chewable tablets “have been part of the pharmacist’s armamentarium for a very long time.” (DTX-39.3)

196. For their sucroferric oxy-hydroxide formulations, Plaintiffs and Teva made chewable tablets using nothing more than customary additives. (DTX-65.5-7; DTX-67.65-66; DTX-75.33; DTX-77.58; PTX-322.12; DTX-171.46)

b. The Prior Art Combination

197. As discussed above, the “chewable tablet” limitation was disclosed and suggested by the ’442 patent.

198. Hergesell teaches that it would desirable to modify the administered composition—

which was described in the ’442 patent—in order to minimize water intake. (Tr. 367:9-25; JTX-0007.3.) A POSA would have been motivated based on this teaching to develop a chewable tablet. (Tr. 366:17-367:25.)

199. The ’465 patent teaches a high load chewable tablet. (Tr. 369:22-370:6; JTX-0004 at 3:11-15, claim 1.) The ’465 patent discloses that patients with renal problems need to limit their liquid intake and thus require a formulation that can be taken with no liquid, or a limited amount of liquid, which is a chewable formulation. (Tr. 367:18-25; JTX-0004 at 1:35-41.) A POSA would have been motivated based on this teaching to develop a chewable tablet. (Tr. 367:18-25.)

200. Since at least 1980, Lieberman taught chewable tablets containing phosphate binders. (Tr. 358:6-13.) Lieberman did not teach away from chewable tablets. (*Id.*)

201. The Lieberman reference disclosed a chewable antacid tablet, which was a phosphate binder. (Tr. 370:8-19; JTX-0008.94.) Antacids are used as phosphate binders and have been in the past. (Tr. 464:3-6.)

202. Lieberman disclosed that the full weight of a chewable antacid tablet could be as much as 600 to 1,500 milligrams. (Tr. 370:20-371:5, 371:13-372:6; JTX-0008.94.)

203. Based on the teachings of Lieberman, a person of skill in the art would know that chewable tablets should have a pleasant taste and mouth feel. (Tr. 373:3-11.) Lieberman teaches inactive ingredients for chewable tablets. (Tr. 372:13-17.) Lieberman teaches that sucrose is commonly used in chewable tablets. (Tr. 372:22-373:2.) Lieberman disclosed a phosphate binder that used mannitol as a sweetener. (Tr. 370:20-371:2; JTX-0008.96.) Mannitol and sucrose are used interchangeably. (*Id.*) Sugar and starch are used for taste masking in bad tasting antacids. (Tr. 372:7-12.)

204. Vifor used standard excipients in developing its tablet. (Tr. 375:10-13.)

205. The ’465 patent provides a reasonable expectation of success in making a high load phosphate binder. (Tr. 468:1-8.)

206. The alleged side effects associated with chewable lanthanum carbonate tablets were due to the lanthanum itself, not the chewable tablet dosage form. (Tr. 468:9-20.)

F. Asserted Dependent Claim 56

207. Asserted claim 56 depends from unasserted claim 55, which recites:

> 55. The method according to claim 27, comprising 700 to 1700 mg iron oxy-hydroxide per dosage form.

(JTX-0001 at claim 55.)

208. Asserted claim 56 recites:

> 56. The method according to claim 55, comprising about 800 mg iron oxy-hydroxide per dosage form.

(JTX-0001 at claim 56.)

1. comprising [700 to 1700 mg / about 800 mg] iron oxy-hydroxide per dosage form.

209. Dr. Chambliss credibly testified that the “comprising 700 to 1700 mg iron oxy-hydroxide per dosage form” and “comprising about 800 mg iron oxy-hydroxide per dosage form” limitations would have been obvious in view of the ’442 patent and/or the prior art combination (Tr. 342:12-344:18.)

a. The ’442 Patent

210. Consistent with the general knowledge in the field at the time of the invention, a POSA would have been motivated to include 800 mg of iron oxy-hydroxide in a single dosage form, in the manner identified in the ’442 patent, in order to reduce pill burden. (Tr. 295:23-296:13, 303:23-304:2, 337:11-23, 456:24-462:14, 657:20-658:6, 713:10-714:8; JTX-0003 at 3:36-55; PTX-0544.1; DTX-0120.; JTX-0007.2; JTX-0004 at 6:56-59, claim 1.)

211. POSA would have had a reasonable expectation of success of being able to

formulate a single dosage form of at least 500 mg using the "powder" of Example 1, especially given the '442 patent's affirmative statement that they "can" be formulated "as such or together with customary drug additives, such as customary carriers or auxiliary materials," including "as granules, tablets, dragees or contained in sachets." (Tr. 296:14-298:12, 332:3-20, 335:17-336:20, 704:13-25; JTX-0003 at 3:9-20.)

212. The '442 patent teaches that the preferred daily dose of the stabilized phosphate binders is approximately 1.5 grams of iron. (Tr. 301:7-24, 335:4-16; JTX-0003 at 3:19-21.) A POSA would know that the phosphate binders would be administered three times per day with meals. (Tr. 290:5-291:15, 301:15-24; JTX-0003 at 3:18-25, claim 12.) Thus, a POSA would recognize that the '442 patent's preferred amount of iron per dosage form is 500 mg (i.e., one-third of the 1.5 g preferred daily dose). (Tr. 335:4-16.) Because the content of iron oxy-hydroxide is approximately 1.6 times the iron content (Uncontested Facts at ¶ 32), each dosage form would preferably contain 800 mg of iron oxy-hydroxide. (Tr. 330:9-18, 335:4-16.)

213. At trial, Plaintiffs agreed that a POSA would understand the '442 patent's teaching of a "preferred" daily dose of 1.5 g of iron to equal an individual dose of 500 mg of iron (i.e., 800 mg of iron oxy-hydroxide) that would be administered 3-times per day with meals. (Tr. 684:6-20, 711:21-712:11; JTX-3 at 3:19-21; PTX-217.1.). Dr. Williams, Plaintiffs' formulation expert, testified that the state of the art recognized that at least 500 mg of oxy-iron compounds was necessary to achieve an effective level of phosphate adsorption. (Tr. 706:17-21.) Dr. Williams also testified that a POSA would understand that the iron oxy-hydroxide compositions of the '442 patent would be taken with food, but he would need to consult a clinician to determine whether that would mean three times per day. (Tr. 684:6-20, 711:21-712:11.) Dr. Rastogi, Plaintiffs' clinical expert, testified that "the assumption is that most of the people have three meals . . . [t]hey

take three meals a day." (Tr. 546:12-17.)

214. It was within the general knowledge of a POSA that phosphate binders are commonly administered with meals three times per day. Renvela (sevelamer carbonate) is a phosphate binder indicated for the control of serum phosphorous in patients with chronic kidney disease on dialysis. (Tr. 713:6-15; DTX-0120.0001.) Renvela was initially approved by FDA in 2000. (DTX-120.0001.) Renvela is available as 800 mg tablets and as a powder in 0.8 g and 2.4 g packets, which are similar to sachets. (Tr. 713:16-714:3; DTX-120.001.) Renvela's starting dose is "0.8 or 1.6 grams to be administered orally three times per day with meals." (Tr. 714:4-8; DTX-120.0001.) Similarly, Renagel (sevelamer carbonate) tablets were to be taken "three times per day with meals" (PTX-0214.1), Phoslyra (calcium acetate) was an oral solution to be taken "with each meal" (PTX-0211.1), and Fosrenol (lanthanum carbonate) chewable tablets had an initial total daily dose of 1500 mg, which patients were instructed to "[d]ivide" and "[t]ake . . . with or immediately after meals." (PTX-0544.1.)

215. It is common sense, and best practice, in the pharmaceutical industry to put the amount of active ingredient to be administered with a meal into a single dosage form (e.g., a single tablet). (Tr. 458:4-6.) Pharmaceutical formulators are motivated to maximize the amount of active in a tablet in order to minimize the number of tablets needed. (Tr. 458:25-459:7.)

216. At trial, Plaintiffs did not present any evidence that a POSA would choose to formulate the compositions of the '442 patent such that the 500 mg of iron to be administered with each meal would be provided in multiple dosage forms (e.g., in two 250 mg tablets) rather than a single dosage form.

b. The Prior Art Combination

217. As discussed above, the "700 to 1700 mg" and "about 800 mg" of iron oxy-hydroxide "per dosage form" limitations were disclosed and suggested by the '442 patent.

218. Hergesell confirmed the general practice of administering a phosphate binder 3 times per day "with meals," as well as doing so with a high load of iron oxy-hydroxide in a single dosage form (i.e., a sachet powder packet) containing approximately 800 mg of iron oxy-hydroxide. (Tr. 301:9-302:, 335:17-23; JTX-7.2.)

219. Hergesell taught and suggested a dosage form containing 500 mg of iron (i.e., 800 mg of iron oxy-hydroxide) based on the reported solubility testing of 500 mg of iron, which a POSA would have understood as a test of the administered dosage. (Tr. 335:17-337:10; JTX-0007.4.) A POSA would also understand the Hergesell powder to contain approximately 21.2% iron (i.e., about 848 mg of iron oxy-hydroxide in a 2.5 g sachet), as that iron percentage was contained in every example of the '442 patent. (Tr. 330:4-8; JTX-0003 at 3:30-10:34.)

220. Prior to the '442 patent, the '079 patent disclosed and suggested a "unitary solid dosage form such as a compressed tablet" containing "500 mg or more" of iron oxy-hydroxide in "each oral dose." (Tr. 303:23-304:11; JTX-0005 at 3:36-55.) At trial, Dr. Williams conceded that the "state of the art" taught as much. (Tr. 706:17-21.)

221. The '079 patent's disclosure of a high load single dosage form "such as a compressed tablet" would have further suggested a chewable tablet form to a POSA. (JTX-0005.3, 3:36-55.)

222. Hergesell teaches the administration of a phosphate binder—which was described in the '442 patent—with meals three times per day. (Tr. 304:12-305:22; JTX-0007.2.) The purpose of the Hergesell study was to test efficacy of the composition when orally administered to patients. (Tr. 304:25-305:14.) Hergesell teaches that 2.5 g of the powder, provided in a sachet (i.e., a single dosage form), was administered three times per day. (Tr. 335:17-336:10; JTX-0007.2.) Patients would open the sachets, mix the powder with about a third of a glass of water, and ingest the oral

suspension. (Tr. 304:25-305:14; JTX-0007.2.)

223. All of the Examples compositions prepared according to the invention of the ’442 patent comprised 21.2% iron. (Tr. 329:25-330:8, 336:21-24; JTX-0003 at 3:30-10:34) Thus, a POSA understand that the powder administered in Hergesell comprised 21.2% iron. (Tr. 336:21-24.)

224. Hergesell reports solubility testing on a sample of the powder comprising 500 mg of iron. (Tr. 336:11-20; JTX-0007.4.) A POSA would understand that the solubility testing would have been performed on a single dosage unit (i.e., the amount of powdered contained in a single sachet). (Tr. 336:11-20, 336:25-337:10.) Thus, a POSA would understand that each sachet of powder administered in the Hergesell study comprised 500 mg of iron, which corresponds to 800 mg of iron oxyhydroxide. (Tr. 336:11-20, 336:25-337:10, 343:22-344:10.)

225. As reflected in the ’079 patent, it would have been within the general knowledge of a POSA they could develop a dosage form comprising 500 mg or more of iron oxy-hydroxide. (Tr. 337:11-339:3.) The ’079 patent teaches orally administering a solid dosage form (e.g., a single compressed tablet or capsule) containing about 50 mg to about 500 mg or more of iron oxyhydroxide compound to a patient afflicted with hyperphosphatemia. (Tr. 303:23-304:11, 337:11-23; JTX-0005 at 3:36-55.) Claims 1 and 14 of the ’079 patent teach an amount effective to bind sufficient ingested phosphate to prevent or alleviate hyperphosphatemia using an oral dosage form of about 500 milligrams of iron oxy-hydroxide. (Tr. 337:11-338:2; JTX-0005 at claims 1 and 14.)

226. As reflected in the ’465 patent, it would have been within the general knowledge of a POSA that a phosphate binders have could be developed as a high load chewable tablet in order to reduce the number of tablets that a person has to swallow or chew. (Tr. 337:11-339:3;

JTX-0004 at 3:11-15, 9:21-44, 13:20-22.) The ’465 patent teaches chewable phosphate binders comprising a high load of lanthanum carbonate. (Tr. 297:21-298:12; JTX-0004 at 3:11-15, 9:21-44, 13:20-22.) The chewable tablets contain up to 1,000 mg of lanthanum, an active ingredient load of 10-40%, and common excipients for making a chewable tablet (including starch and sucrose). (Tr. 295:23-296:13, 297:21-298:12, 339:10-18; JTX-0004 at 9:21-44, 13:20-22, claim 1.) Claim 1 of the ’465 patent discloses a chewable lanthanum carbonate tablet from about 200 milligrams to 1,000 milligrams. (Tr. 338:3-19; JTX-0004 at claim 1.) The ’465 patent teaches that the advantage of higher strength tablets is reduced overall pill burden, which is an important issue affecting patient compliance. (Tr. 298:5-8, JTX-0004 at 13:20-22.)

227. The ’465 patent teaches a chewable tablet that weighs 4,168 mg, and Dr. Chambliss has made chewable tablets weighing five grams (Tr. 339:19-340:12; JTX-0004 at 9:21-44.)

G. There Is No “Teaching Away” that Makes Example 1 Not Obvious to Try or Overcomes the Strong Motivations to Combine the Prior Art

1. The Hergesell “formula” would not have taught away from Example 1

228. A POSA would have recognized the “formula” provided in Hergesell to be non-standard and erroneous. (Tr. 402:22-403:17.) Dr. Chambliss and Dr. Harris both did not understand the meaning of the “l” or “l/m” in the Hergesell formula. (Tr. 403:12-17.) A POSA would have recognized that the authors of Hergesell were medical doctors rather than chemists. (Tr. 402:22-403:7.) A POSA would not have relied on or given weight to the “formula” provided in Hergesell. (*Id.*) Dr. Chambliss stated that the formula in Hergesell is not complete. (Tr. 407:18-21.)

229. A POSA would understand that the non-iron oxy-hydroxide portion of the Hergesell formula is $C_6H_{10}O_5$. (Tr. 404:12-408:9.) The formula $C_6H_{10}O_5$. is consistent with starch (used in Example 1), amylopectin (used in Example 7), and white dextrin (used in Example 8.) (*Id.*) The formula $C_6H_{10}O_5$. is not consistent with saccharose (the only carbohydrate used in

Example 6) or humic acid (the only carbohydrate used in Example 9). (*Id.*)

230. Example 7 exhibited significantly worse *in vitro* phosphate binding capacity than Examples 1 and 8, and amylopectin is not a common excipient for pharmaceutical formulations. (Tr. 480:18-25.) Thus, to the extent a POSA relied on the Hergesell "formula," they would be directed to Examples 1 (using saccharose and starch) and 8 (using dextrin), both of which demonstrated essentially identical *in vitro* capacity for binding inorganic phosphate. (Tr. 398:18-23, 411:10-12.)

2. A POSA would have used Example 1 of the '442 Patent

231. A POSA considering the '442 patent would choose to pursue development of Example 1. (Tr. 292:2-293:3, 293:15-295:3, 396:13-18.)

232. Of the Examples containing carbohydrates matching the formula, Plaintiffs essentially only point to Examples 6 and 8 as allegedly better "starting points" than Example 1. (Tr. 399:11-20, 662:21-664:16.)

233. Example 1 is the first example in the '442 patent and the most likely place for a POSA to start. (Tr. 396:13-18.)

234. Example 1 is the predominant example in the '442 patent and is used throughout the examples. (Tr. 292:11-295:3, 397:2-414:2, 478:1-480:25.) Sucroferric oxy-hydroxide, the material of Example 1, is used in Examples 1-5, 12-13, and 16. The composition used in Example 1 of the '442 patent is the only composition used in multiple other examples of the '442 patent. (Tr. 292:13-15.)

235. Example 1 is the only composition that is specifically referred to as a "powder" (i.e., a dosage form), and it would be viewed as the only composition of the examples which would not require further formulation development. (Tr. 290:15-293:3.)

236. Example 12, which uses the material of Example 1, is the only Example that refers to the iron oxy-hydroxide as "stabilized." (Tr. 293:24-294:8, 392:14-22.)

237. Examples 4 and 5, which only use the material of Example 1, are the only Examples that disclose binding capacity for organic phosphate.

238. Example 1 is the only example in the '442 patent that mixes the material with other ingredients (Tr. 293:18-23) and Example 16 is the only example that mixes the material with food (Tr. 294:13-16) for administration to an animal. In Example 16, the powder from Example 1 was mixed into pellets and fed to rats. (Tr. 294:21-295:3.) The purpose of an orally-administered phosphate binder is to bind with phosphates in a meal, so they are absorbed. (Tr. 294:19-21.)

239. Because Example 1 contains both saccharose *and* starch, a POSA would recognize it as having the best profile in terms of taste/palatability and processability/flowability and would be ready to go as a dosage form. (Tr. 284:11-285:2, 292:20-293:3, 461:23-462:1, 478:5-12.)

240. A POSA would understand that a powder must be flowable in order to process properly. (Tr. 293:22-23.) A POSA would recognize that using sucrose as the only stabilization agent (as in Example 6) would result in an unsuitable composition that becomes too sticky during processing. (Tr. 479:11-15.) When sucrose is spray-dried, it becomes sticky and will need a carbohydrate, such as starch, to keep it from being too sticky. (*Id.*) When Plaintiffs attempted a composition with sucrose as the only stabilization agent, the composition was too sticky for processing, which was resolved by the addition of starch to improve flowability (DTX-65.3; DTX-80.11-12, 23; DTX-82.13)

241. Iron oxy-hydroxide must be stabilized so it does not deteriorate over time. (Tr. 294:9-12.) A POSA would also recognize that while dextrin (Example 8) is not as sweet as saccharose, and that both dextrin and sucrose (Example 6) would, without the addition of starch,

be less effective at preventing the iron oxy-hydroxide from destabilizing over time. (Tr. 479:16-480:16.)

H. The Asserted Claims Recite Nothing More than the Inherent Properties of the Composition(s) of the ’442 Patent

242. Dr. Chambliss offered unrebutted testimony that the “essentially non-bioabsorbable” property of the iron oxyhydroxide (Claim 29) and the “iron release rate of below 2.5% w/w” (Claim 30) are the natural result of the composition described in Example 1 of the ’442 patent. (Tr. 289:17-290:4, 354:14-357:5.)

243. The “essentially non-bioabsorbable” property of iron oxyhydroxide is a natural result of the composition described in Example 1 of the ’442 patent. (Tr. (Chambliss) 289:17-290:4, 354:14-18.) Example 1 is the only example in the ’442 patent that teaches a composition having stabilized beta iron oxyhydroxide. (Tr. 289:17-290:4, 299:5-19, 299:24-300:4; JTX-3.1, JTX-3.2, .6.) The ’442 patent also discloses that “the absorption materials comprising insoluble stabilised polynuclear beta-iron hydroxide” are “insoluble” and “release little iron.” (JTX-3.2; Tr. 299:5-11; *see also* Tr. 356:5-23.) Dr. Chambliss explained that insolubility is an inherent property of stabilized iron oxyhydroxide. (Tr. 395:23-25.) As Dr. Chambliss testified, the inherent insolubility of the stabilized iron oxyhydroxide of the ‘442 patent is directly correlated with decreased iron absorption and low iron release. (Tr. 299:12-19, 300:20-24 (“If it’s insoluble, the release will be low. If the release is low, the adsorption will be low.”), 346:1-4.) Accordingly, non-bioabsorbability was a natural result of the insoluble active ingredient. (Tr. 289:17-290:4.)

244. The ’251 patent also confirms that iron oxyhydroxide inherently is essentially not absorbed by the human body. (JTX-001.3, 4:59-67; Tr. 326:4-21, 350:17-351:1.) As Dr. Chambliss opined, the ’251 patent also states that its compositions “are indicated for use in the known indications” or known uses of iron oxyhydroxides, which includes the compositions of the ’442

and ’079 patents. (JTX-001.7, 11:39-43; Tr. 326:17-327:10.)

245. Dr. Rastogi’s reliance upon only the characteristics of the API to conclude that the drug product would be “essentially non-bioabsorbable” confirms that bioabsorbability is an inherent property of the API. Specifically, Dr. Rastogi concluded that Teva’s ANDA product “is also essentially non-bioabsorbable and meets claim 29” because its API – sucroferric oxyhydroxide – is “insoluble or practically insoluble, and therefore, not absorbed,” without any consideration of its manufacturing processes. (Tr. (Rastogi) 102:11-19; DTX-152.0006.) In rendering his infringement opinion, Dr. Rastogi likewise relied upon Teva’s statements that “[i]ron oxyhydroxide is special due to the fact that [it] is not available in soluble form to be absorbed in the [gastrointestinal] tract.” (DTX-177.0010; *see also* Tr. 111:2-17.)

246. Dr. Philipp coauthored an article titled “PA21: A novel phosphate binder for the treatment of hyperphosphatemia in chronic kidney disease” (DTX-62) (“Geisser”), which “report[ed] the results of an open-label, Phase I study in which PA21 was administered to three predefined groups: non-dialysis CKD patients, patients requiring maintenance hemodialysis, and healthy subjects.” (DTX-62.002; Tr. (Philipp) 253:5-12.) As Geisser described, 24 subjects received a 10 g daily dose of radiolabeled PA21 for 21 days. (DTX-62.003.) Geisser characterized iron uptake as “very low” and reported that “the median uptake was 0.04% (range 0 – 0.44%) across both CKD subgroups, compared to the 0.43% range (range 0.16% - 1.25%) in the healthy subjects.” (DTX-62.005, .007; Tr. (Chambliss) 359:12-360:6.) Geisser referenced Hergesell as another study in which PA21 had been administered in patients. (DTX-62.007.)

247. Geisser also referenced an earlier *in vitro* study of PA21: “PA21 has also been found to be poorly soluble *in vitro*, with minimum iron release at pH greater than 2.5, and would thus be expected to have a low toxic potential.” (DTX-62.002; Tr. (Chambliss) 359:12-360:6.) As

Dr. Chambliss explained, the low pH values used in this in vitro study mimicked the pH of the gastrointestinal tract. (DTX-62.002; Tr. 359:12-360:6.) While reviewing Geisser (DTX-62), Dr. Philipp testified that the *in vitro* data of PA21 described in this article was the same *in vitro* data from testing of the Example 1 Composition. (DTX-62.001, .002, .008; Tr. (Philipp) 253:5-12, 253:20-254:8, 255:3-6.) As Dr. Chambliss explained, Geisser confirmed that PA21 minimum iron release in vitro was consistent with the very low iron uptake shown in Geisser's *in vivo* study. (Tr. 359:12-360:6.) Dr. Chambliss stated that both Hergesell and Geisser confirmed his opinion that the inherent insolubility of the Example 1 Composition rendered claim 30 obvious. (Tr. 356:5-23, 360:7-14.)

248. According to Dr. Rastogi, *in vitro* dissolution testing can show that the iron is "essentially non-bioabsorbable." If performed at a pH that mimicks the gastrointestinal tract, dissolution testing can provide results that would be directly correlated with bio-absorption. Dr. Rastogi agreed that, when dissolution testing of iron oxyhydroxide at the "appropriate pH" of an iron oxyhydroxide product indicated "that there would be very minimum, if any, iron release," this would indicate "very minimum, if any" iron absorption. (Tr. (Rastogi) 113:20-23.) As Dr. Rastogi opined, if dissolution testing of iron oxyhydroxide uses pH that mimicks the fed state – i.e., a pH of 4.5 to 6.8 – and the testing shows no iron release, then there would be no iron to be absorbed. (Tr. (Rastogi) 124:3-16.) Dr. Rastogi also stated that he had relied upon Dr. Harris's evaluation of *in vitro* solubility studies and Dr. Harris's conclusion that the iron oxyhydroxide is "poorly soluble" to opine that the Teva ANDA product would be essentially non-bioabsorbable. (Tr. 128:11-25.)

249. Vifor's FDA submissions and internal documents confirm that being essentially non-bioabsorbable is an inherent property of PA21. (Tr. 318:12-21, 350:17-354:8; DTX-47.0006;

DTX-73.11, 56; DTX-76.11, 13, 15, 23, 32, 65; DTX-77.12, 21, 91; DTX-78.46, 460; DTX-80.11-13, 23; DTX-83.7, 9, 11, 26, 28, 30, 32.)

250. While reviewing Vifor's Investigational Medicinal Product Dossier for PA21 dated April 29, 2011 (DTX-67), Dr. Philipp testified that PA21-1 was the original drug substance formulation, which was used in the Hergesell study and had an active pharmaceutical ingredient that was referred to as XR-500. (DTX-67.0012; Tr. (Philipp) 265:18-266:21; *see also* Tr. 307:13-19 (Chambliss).)

251. When seeking FDA approval for Velphoro, Vifor relied on Hergesell's iron absorption results. (Tr. (Chambliss) 318:18-21.) Specifically, Vifor's Investigator's Brochure for PA21, which was provided to its clinical trial investigators and to the FDA, relied upon the Hergesell publication when stating that the efficacy of the iron-based phosphate binders had been demonstrated in a four-week in vivo study of uremic patients. (Tr. 318:23-319:6; DTX-83.09.) This Investigator's Brochure demonstrated that, based on the Hergesell publication and its study results, Vifor expected and found no clinically significant absorption of iron, and Vifor characterized the API as having "characteristics of insolubility and degradation." (Tr. 319:7-11, 352:3-20; DTX-83.09, .11, .26, .28, .30., 32.) And a POSA would have interpreted the Hergesell data consistently to expect that administration of PA21 would have resulted in no clinically significant absorption. (Tr. 319:12-18, 352:3-20; DTX-83.09.) As Dr. Chambliss testified, Vifor's Investigator Brochure for PA21 confirmed that no clinically significant iron absorption was an inherent property of the composition of Example 1 of the '442 patent. (Tr. 352:21-353:1; DTX-83.09.)

252. In its NDA for Velphoro, Vifor represented to FDA that PA21 had an inherent property of no clinically significant iron absorption. (Tr. (Chambliss) 353:21-354:8, 482:3-483:12;

DTX-80.12; DTX-73.11, .56.) In the Quality Overall Summary of the Drug Substance, Vifor stated that PA21-2 had been shown to have similar properties to PA21-1 and "essentially no difference in the pharmaceutical effect or toxicity." (Tr. 353:21-354:8; DTX-80.12.) Likewise, Vifor's Investigational Medicinal Product Dossier (DTX-77) – the European counterpart to the Investigator Brochure submitted to FDA (DTX-83) – referenced Hergesell's results to support Vifor's expectation that no clinically significant amount of iron absorption would result from administration of PA21, and stated that PA21-1 and PA21-2 had comparable iron release values. (Tr. 353:2-12; DTX-77.19, .21, .91.) As Dr. Chambliss testified, this European dossier confirmed that PA21 – i.e., the Example 1 Composition – had an inherent property of no clinically significant iron absorption. (Tr. 353:13-20; DTX-77.19, .91.)

253. Vifor's FDA submissions and internal documents confirm that an iron release rate of below 2.5% is an inherent property of PA21. (Tr. 361:14-363:10; DTX-0076.15, 23, 86; DTX-77.12, 19, 21; DTX-80.11-13, 23; DTX-83.9, 26, 28, 30, 32.)

254. In another submission to the European Medicines Agency (EMA) concerning PA21, Vifor described *in vitro* testing of PA21 at pH of 1.2 and found that the it resulted in iron release of 6.8%. (DTX-0076.0086; Tr. 361:14-25.) Vifor referenced Hergesell, which showed that, after 5 hours, there was a 0% iron release rate at pH 8 and 2.1% percent iron release rate at pH 3. (DTX-0076.0086; Tr. 361:14-25.) This document confirmed that, at pH 3, the compound was insoluble. (Tr. at 362:1-5.) Furthermore, as Dr. Chambliss concluded, this document compared the iron release rate for PA21-1 and PA21-2 were about 5.4% and 6.2% respectively, and found that their rates were comparable. (Tr. at 362:6-363:6.) Dr. Chambliss opined that these disclosures confirmed that the inherent insolubility of the PA21-1—the product of Example 1 of the 442 patent—rendered the limitation of claim 30 obvious. (Tr. 363:3-10.)

255. In the submission to the EMEA, Vifor also stated that the PA21-1 drug substance was used in Hergesell. (DTX-76.23.) Further, Vifor indicated that there was no meaningful difference in the iron release as between Velphoro (PA21-2) and the material described in Example 1 of the ’442 Patent (PA21-1): “PA21-2 has been shown to have the same specifications as PA21-1 with essentially no difference in the pharmacological effect or toxicity” (DTX-76.11).

256. In a clinical study report, Vifor stated that “[t]he comparability of the two drug substance formulations [PA21-1 and PA21-2] was demonstrated by comparison of iron release” among other properties.” (DTX-78.63.)

257. Vifor’s internal documents also showed that minimal iron absorption was an inherent property. (Tr. (Chambliss) 350:17-351:1; DTX-47.0006.) For example, a June 2004 Vifor document titled “Project PA21: Business Analysis and Planning” explained that, like the Example 1 composition, PA21 was a mixture of iron oxyhydroxide with sucrose and starch. (Tr. 351:2-18; DTX-47.0006.) This document further noted that two patents had been filed “around PA21” – one of which Dr. Philipp identified as the ’442 patent – and that the Hergesell publication provided more details concerning this composition. (Tr. (Philipp) 249:2-250:14, (Chambliss) 351:2-18, 351:23-352:1; DTX-47.0006.) Additionally, Vifor’s internal document also cited to Hergesell to state that, based on study data, PA21 may be administered without any clinical concerns. (Tr. 351:2-22; DTX-47.0006.)

258. Vifor failed to present any evidence or testimony that manufacturing variables such as particle size or spray drying would affect the bioabsorption or iron release properties of an iron oxyhydroxide product. (Tr. 481:16-482:2.) As Dr. Chambliss noted, Vifor’s represented to FDA and other regulatory agencies that particle size and spray drying would not affect these properties. (*Id.*) Specifically, Vifor’s Quality Overall Summary for the drug product stated that because the

drug substance – iron oxyhydroxide – is "practically insoluble, the particle size of the [drug substance] has no impact on bioavailability." (DTX-73.11, .56; Tr. 482:3-23.) As Dr. Chambliss explained, this confirms that the particle size as no impact on the iron release rate. (Tr. 482:3-483:12.)

259. Vifor attempted to establish that some material sent to Hergesell may have been PA21 and may have been spray dried, but the documents presented during cross-examination of Dr. Chambliss lack any foundational testimony or sponsoring witness, and the validation report is neither signed nor dated. (PTX-505; *see* Tr. 443:20-448:16, 472:19-475:6; PTX-505, PTX-507; PTX-539.)

260. Vifor focused on product 8b described in Example 8 and Table 9a of the '251 patent. (*See* Tr. 417:10-13; JTX-1.8, 14:40-59, Table 7.) However, product 8b is not an embodiment of the '251 patent claims because it does not contain starch. (Tr. (Chambliss) 417:15-21; JTX-1.8, Table 7.) Every product described in Example 8 as containing both saccharose and starch as a stabilizer (i.e., products 8a, 8d, 8e, 8f, and 8g), as required by claims 29 and 30, reported release rates of 1.8% or lower. (Tr. 422:1-16; JTX-1.8, 14:39-59, Tables 7, 9a, 9b.)

261. Plaintiffs presented PTX-597, a German language notebook page, to Dr. Chambliss on cross-examination, but Dr. Chambliss found that the document provided no reliable or credible information to draw any scientific conclusions. (*See* Tr. 428:25-432:11).

262. Dr. Rastogi stated that the '251 patent does not indicate what "clinically significant amount" means. (Tr. 121:19-23.)

I. The Alleged Secondary Considerations Do Not Support Non-Obviousness

1. No Long-Felt Unmet Need

263. Dr. Rastogi opined that Velphoro met a long-felt need for a phosphate binder that was safe, efficacious, and well tolerated. (Tr. 492:11-493:19.) But such a need did not exist, and

other products already met any alleged need. (Tr. (Fadem) 730:17-22.)

264. Several calcium-free phosphate binders, which had been approved by FDA based on their safety and efficacy profiles, were available prior to Velphoro's launch. (Tr. (Rastogi) 534:9-15, 535:7-18.) For example, prior to November 2007, sevelamer and lanthanum were approved by the FDA for the treatment of CKD and hyperphosphatemia. (*Id*. at 535:10-14.) Phosphate binders including calcium carbonate were also commercially available years before Velphoro's launch. (*Id*. at 535:15-18.) Dr. Fadem agreed that all of these phosphate binders were safe and effective. (Tr. (Fadem) 729:20-730:3.)

265. Sevelamer and lanthanum, which are both calcium-free phosphate binders, were safe binders. (Tr. (Rastogi) 502:14-23, 542:2-5; (Fadem) 731:3-6, 730:24-731:6, 736:25-737:5.) In fact, Dr. Rastogi still prescribes sevelamer about 50% of the time. (Tr. (Rastogi) 540:19-541:3.)

266. Vifor reported in its 2018 Operating Plan that prescribing physicians perceived Velphoro to be "interchangeable" with other phosphate binders – Renvela, Fosrenol, Auryxia, and calcium acetate – based on factors including "[long term] safety profile." (DTX-777.0018; *see also* Tr. (Mulhern) 603:12-25.) Vifor's 2018 Operating Plan also showed that Renvela and Fosrenol had higher scores for "[long term] safety profile" than Velphoro. (*Id.*)

267. Dr. Rastogi emphasized that calcium-based phosphate binders had significant issues, including risk of vascular calcification. (*See* Tr. (Rastogi) 497:21-499:24.) Yet, calcium-based phosphate binders are still commonly used and considered to be a first-line therapy. (Tr. (Rastogi) 501:8-12, 539:13-21; (Fadem) 731:7-11.) Calcium-based binders have other advantages, including being available as an over-the-counter medication – i.e., not requiring a prescription – and being inexpensive. (Tr (Rastogi) 536:19-537:16.)

268. Additionally, calcium-free phosphate binders like lanthanum and sevelamer were

commercially available and filled the alleged need before Velphoro's introduction into the market. (Tr. (Rastogi) 508:22-509:18, 542:2-5; (Fadem) 730:17-731:6.) Dr. Rastogi even admitted that sevelamer filled this need. (Tr. (Rastogi) 539:8-12.) His published literature also demonstrated that sevelamer was associated with prevention of calcification, as well as less progression of coronary artery and aortic calcification as compared to calcium-based binders. (*Id*. at 538:20-539:12.) Likewise, Dr. Rastogi's 2014 publication in *Therapeutic Advances in Cardiovascular Disease* noted that lanthanum was associated with less progression of vascular calcification as compared to calcium-based phosphate binders. (*Id*. at 542:20-543:22.) And while Dr. Rastogi asserted that lanthanum may have neurotoxicity issues, he admitted that no connection has been made between lanthanum and neurotoxicity. (*Id*. at 544:8-11.)

269. Velphoro did not fill a need for a phosphate binder with decreased gastrointestinal issues. All commercially available phosphate binders have some gastrointestinal effects. (Tr. (Rastogi) 536:9-12, 536:16-18, (Fadem) 730:4-10.) Yet, an article relied upon by Vifor's expert included a table surveying, *inter alia*, the disadvantages of six commercially available phosphorus binders. (DTX-729.0006; Tr. (Mulhern) 597:10-18; 599:14-23.) Notably, this table highlighted "gastrointestinal side effects" as a disadvantage only with respect to Velphoro. (DTX-729.0006; Tr. (Mulhern) 599:17-19.) Likewise, an article relied upon by Dr. Rastogi stated that, despite Velphoro's introduction to the market, "gastrointestinal tolerance" remained an "unsolved problem" with respect to phosphate binders. (DTX-1019.0011; Tr. (Rastogi) 547:13-548:13.)

270. Dr. Fadem credibly explained that it was "standard practice" to have patients take phosphate binders three times a day with meals, and that "binders are effective if you take them with your meals." (Tr. (Fadem) 730:11-22.) This supported Dr. Fadem's conclusion that prior art phosphate binders had already met the alleged long-felt but unmet need. (*Id.*)

271. To the extent Velphoro met an alleged need for a phosphate binder with higher efficacy, its stabilized API, which was already known in the prior art, was responsible for its efficacy. (Tr. (Rastogi) 515:2-516:2.) Velphoro's stabilized iron oxyhydroxide API was known for years prior to the priority date of the '251 patent and Velphoro's launch. (Tr. (Chambliss) 289:6-290:4; (McDuff) 743:15-744:5, 747:17-24; *see generally id.* at 746:24:748:1.) The '442 patent is directed to stabilized oxyhydroxide. (Tr. (Chambliss) 289:6-16, (Mulhern) 634:11-14; JTX-003.1 at Abstract, 1:48-52.).

272. Prior art powder-based phosphate binders were also available. (Tr. (Chambliss) 297:21-298:8.) Sevelamer is available in both pill and powder form, (Tr. (Rastogi) 535:10-14, 541:4-22.), and Dr. Rastogi testified that he prescribes the powder form to patients about 20% of the time. (*Id*. at 541:7-22.)

273. Velphoro did not fill the alleged need for a phosphate binder with better tolerability and compliance or lower pill burden. (Tr. (Fadem) 730:17-731:14; *see* Tr. (Rastogi) 508:6-13.) Even after Velphoro's launch, the industry recognized that the issue of high pill burden remained unsolved. (Tr. (Rastogi) 547:13-548:13.) Dr. Rastogi relied upon an article by Dimitra Nastou titled "Next-Generation Phosphate binders: Focus on Iron-Based Binders" ("Nastou"). (*Id*. at 547:13-15; DTX-1019.) However, Nastou stated that Velphoro was "not expected to represent a quantum leap," and "[t]wo unsolved problems remain: the high pill burden (three to four per day) and gastrointestinal tolerance." (*Id*. at 547:13-548:13; DTX.-1019.0011.)

274. Pill burden and tolerability did not differentiate Velphoro from its competitors. In its 2018 Operating Plan, Vifor concluded that prescribing physicians perceived Velphoro as "interchangeable" with other phosphate binders – Renvela, Fosrenol, Auryxia, and calcium acetate – based on factors including "long term serum phosphorous control" and "patient compliance."

(Tr. (Mulhern) 603:12-25; DTX-777.0018.) Vifor also recognized that "[e]fficacy drives behaviors, pill burden does not." (*Id*. at 604:22-605:8; DTX-777.0018.) In fact, in 2018, Vifor discarded its marketing message focused on pill burden. (Tr. (McDuff) 747:2-8; DTX-324.0013.)

275. Phosphate binders with pill burden similar to and even less than Velphoro's pill burden existed before Velphoro's launch. (Tr. (McDuff) 747:2-8.) For example, lanthanum launched about ten years before Velphoro and competes with Velphoro in the market (Tr. (Mulhern) 593:23-594:4), and has a starting dose that is the same as Velphoro's starting dose. (Tr. (Rastogi) 546:6-11; Uncontested Facts at ¶ 13.) Because lanthanum is available in 500-mg, 750-mg, and 1,000-mg doses, its starting dose can be achieved with only two tablets, which is less than Velphoro's starting dose of three 500-mg tablets. (*See* Tr. (Mulhern) 594:13-19, 595:12-18; PTX-544.2; DTX-0264.2; Uncontested Facts at ¶ 13.) As both parties' experts confirmed, a patient can achieve a daily 1,500 mg dose through 3 tablets of Velphoro, i.e., one with each meal, and this dose may be titrated up to include even more pills (Tr. (Fadem) 214:6-18; (Rastogi) 546:6-20, 547:10-12; Uncontested Facts at ¶ 13.) Industry publications, including an article referenced by Ms. Mulhern, confirm that the pill burden of lanthanum is similar to and even lower than that of Velphoro. (Tr. (Mulhern) 597:10-598:12; DTX-729.0006 (listing the average number of pills as 3 for lanthanum and 3.75 for sucroferric oxyhydroxide (Velphoro)).)

276. Dr. Rastogi's assertion that Velphoro met a long-felt but unmet need for lower pill burden is undercut by Aurxyia's relatively superior performance. (Tr. (Fadem) 730:17-731:14.) Vifor's research showed that reduced pill burden was not an advantage for Velphoro as compared to Auryxia. (Tr. (McDuff) 747:2-8; DTX-330.0011.) In May 2019, Vifor considered purchasing Auryxia, and this potential acquisition was referred to as "Project Apple." (DTX-330; Tr. (Mulhern) 605:17-24, 606:3-11.) Based on data from 203 nephrologists, Vifor concluded that pill

burden provided Velphoro only a slight advantage over some competitors, such as Renvela and calcium acetate, while providing no advantage over Aurxyia. (DTX-330.11; Tr. (Mulhern) 606:3-607:14.) This Project Apple study showed that prescribing physicians perceived Velphoro and Auryxia to have "almost equal" pill burden. (DTX-330.11; Tr. (Mulhern) 607:12-14, 607:21-608:5.) Vifor placed a "thumbs down" graphic on this comparison of Velphoro's tolerability, convenience, affordability, and coverage. (DTX-330.11; Tr. (Mulhern) 608:6-8.) In this Project Apple presentation, Vifor also reported that Velphoro had high discontinuation rates as compared to Auryxia and Renvela. (DTX-330.0012). Moreover, Vifor reported that two of the top three reasons for Velphoro discontinuation was "tolerability" and "formulation issues." (*Id.*).

2. No Surprising or Unexpected Results

277. Dr. Rastogi opined that he had noted two unexpected results from Velphoro: (1) its high-loading dose in a "relatively reasonably sized tablet" with minimal adverse gastrointestinal events, and (2) its efficacy and minimal free iron release. (Tr. (Rastogi) 512:13-514:11.)

278. Velphoro did not exhibit any unexpected results. (Tr. (Fadem) 731:15-732:2.) As Dr. Fadem explained, there was significant prior art like Hergesell that discussed effective phosphate binders for uremic patients. (*Id.*; JTX-7) There were also other available safe and effective iron and non-iron based products, such as lanthanum, a non-iron based, high-loading chewable tablet. (*Id.*; *see also* Tr. (Mulhern) 603:4-25; DTX-777.0018.)

279. Dr. Rastogi relied upon a retrospective study of Velphoro by Coyne (DTX-1020) that was sponsored by Vifor, and he admitted that this retrospective analysis "has limitations." (Tr. (Rastogi) 510:22-23; 530:18-22; 531:8-11; DTX-1020.9-.10.) One of these limitations was the difficulty in following the patients studied. (*Id.* at 530:23-531:11.) Dr. Rastogi's discussion of Coyne was also unrelated to compliance. Dr. Rastogi characterized Coyne's results as "increasing the number of patients achieving phosphorous levels [of] 5.5 or below" and doing so "with almost

half the number of pills." (*Id*. at 511:6-23; DTX-1020.2.) However, the Coyne study was a proof of concept study to show that the drug worked if used properly. (*Id*. at 531:12-533:10.) Dr. Rastogi admitted that a proper study would include a two-arm randomized control trial with a proper titration. (*Id*. at 533:11-14.) That is not what was done in the Coyne study. (*Id*. at 533:15-17.)

3. No Commercial Success

280. Velphoro was not commercially successful. (Tr. (McDuff) 744:6-15; *see also id.* at 743:15-744:5.) As Dr. McDuff testified, in view of the size of the phosphate binder market, Velphoro had weak market penetration and failed to capitalize on its market opportunity. (*Id*. at 752:20-753:4.)

281. Dr. McDuff extensively reviewed Vifor's internal business records, analyzed deposition testimony in this case, and consulted with Teva's technical experts to form his opinions concerning Velphoro's lack of commercial success and the absence of a nexus between Velphoro and the asserted claims. (Tr. (McDuff) 744:16-20.)

a. The Relevant Market Included Calcium-Based and Calcium-Free Binders

282. In an effort to inflate Velphoro's market share, Ms. Mulhern compared Velphoro's performance to only calcium-free phosphate binders and improperly excluded calcium-based phosphate binders. (Tr. (Mulhern) 569:13-21, 570:4-19; (McDuff) 744:21-745:17.) When comparing Velphoro to the complete phosphate binder market, the evidence shows that Velphoro's share of prescriptions was only 6.7% – as opposed to 10.2% of the calcium-free phosphate binder submarket – between January and September 2019. (Tr. (McDuff) 744:21-745:17; DTX-313-M.)

283. The relevant market of Velphoro included both calcium-based and calcium-free phosphate binders. (Tr. (Mulhern) 568:8-22, 616:14-617:2; (McDuff) 745:2-17.) In her analysis, Ms. Mulhern applied a market definition that was too narrow because she excluded calcium-based

phosphate binders. (Tr. (McDuff) at 744:21-745:17.) As Dr. McDuff explained, the relevant market includes both calcium-free and calcium-based phosphate binders. (*Id*.) Vifor's own market analyses relating to Velphoro support Dr. McDuff's market definition. (*Id.*; DTX-512.0005 (evaluating the phosphate binder market and showing that calcium-based phosphate binders comprise 60% of the market and calcium-free phosphate binders comprise 40% of the market); DTX-330.11 (comparing Velphoro to phosphate binders generally, including calcium acetate).) Moreover, Vifor's expert, Dr. Rastogi, compared Velphoro to calcium-based binders when providing opinions on long-felt but unmet need and unexpected results. (Tr (Rastogi) 497:21-498:22.) Dr. Rastogi's understanding of the market is consistent with Dr. McDuff's opinions.

b. Velphoro Was a Not Commercial Success

284. Within the complete phosphate binder market, Velphoro performed in the "middle of the pack at best" based on its total prescriptions between March 2014 and September 2019. (Tr. (McDuff) 748:7-24; DTX-148-K; DTX-697.)

285. Even considering only the calcium-free phosphate binder submarket, Velphoro was still outperformed by four other phosphate binders. (DTX-313-M; DTX-697; Tr. (McDuff) 748:7-24.) In forming her opinions, Ms. Mulhern testified that she considered Velphoro's sales and sales growth in the context of the phosphate binder market. (Tr. (Mulhern) 565:14-21, 566:10-20.) Vifor asserts that Velphoro was commercially successful based on its sales growth from launch. (*See id*. at 566:10-20; (McDuff) 753:16-23.) However, Ms. Mulhern did not consider Velphoro's performance after September 2019. (Tr. (Mulhern) 618:11-14.) In fact, the recent decrease in Velphoro's net sales confirms that it is not commercially successful. As Vifor reported in its August 6, 2020 press release titled "Vifor Pharma Reports Continued Growth in H1 2020," Velphoro's net sales decreased by 8.9% in the first half of 2020. (Tr. (Mulhern) 618:19-619:19; DTX-1063.0002.) The simultaneous increase in Vifor's sales of other nephrology products – such

as Venofer, Retacrit, and Mircera – undercuts Ms. Mulhern's attempt to attribute this recent decrease in Velphoro's sales to current events. (DTX-1063.0002; Tr. (Mulhern) 638:7-14.)

286. Velphoro had weak market penetration and failed to capitalize on its market opportunity. (Tr. (McDuff) 752:20-753:4.) While Ms. Mulhern emphasizes marketplace penetration as indicative of success (Tr. (Mulhern) 575:3-11), her own analyses demonstrate that Velphoro's average prescription share from its launch until 2019 was only 3.2%, which was smaller than five other phosphate binders on the market. (*Id*. at 617:10-618:6; DTX-313-M.) Third party analysts such as UBS also characterized Velphoro's market penetration as "extremely limited." (DTX-325.0001; Tr. (Mulhern) 633:7-12.)

287. Auryxia, which Ms. Mulhern admits was a "particularly close competitor," outpaced Velphoro based on its share of prescriptions by 2017 despite launching nine months after Velphoro in December 2014. (DTX-313-M; Tr. (Mulhern) 567:19-21, 575:12-17, 621:12-622:5, 622:13-23.) In fact, when considering whether to acquire Auryxia in 2019, Vifor stated that it expected Auryxia to be more commercially successful than Velphoro. (DTX-330.19; Tr. (Mulhern) 623:3-11.) Auryxia's "apparent superiority" undermines Ms. Mulhern's emphasis on late market entry as an excuse for Velphoro's poor performance. (Tr. 623:12-16.)

288. In the pharmaceutical industry, it is not uncommon for brand products like Velphoro to compete with generic products, and prior to launching Velphoro, Vifor was aware that it would be competing with generic products. (Tr. (Mulhern) 620:11-19.)

289. Velphoro's missed sales projections confirm that Velphoro was not a commercial success. For example, whereas Vifor projected in its 2015 Brand Plan that Velphoro would have a 2.6% share of the phosphate binder market by December 2014 (DTX.319.0005; Tr. 630:15-631:6), Velphoro's actual market share was only 1% during that same time (Tr. 631:11-17; DTX-313-M.)

When forming her opinions, Ms. Mulhern did not consider Velphoro's failure to meet sales forecasts and projections even though she admitted that this was reasonable criteria to consider for a commercial success analysis. (Tr. (Mulhern) 629:17-630:14.)

290. Velphoro also missed external sales projections. For example, third party UBS emphasized Velphoro's disappointing launch in a July 2014 article titled "Galenica, Disappointing Launches Downgrading to Sell." (DTX-325.0001; Tr. (Mulhern) 632:12-19.) According to UBS, Velphoro had "extremely limited market penetration" and was estimated to generate only $9.9 million in sales, far below the initial UBS projection of $30 million. (DTX-325.0001; Tr. 633:7-12.)

291. While return on investment can be relevant to commercial success (Tr. (Mulhern) 626:25-627:4), Ms. Mulhern did not consider whether Vifor earned a positive return on its investment in Velphoro. (*Id*. at 629:8-10.) Specifically, she did not take into account Velphoro's development costs (*Id*. at 627:5-8), and did not even request such information from Vifor (*Id*. at 628:23-25.)

292. Ms. Mulhern did not consider that Vifor suspended Velphoro's development for three years due to high production costs. (Tr. (Mulhern) 628:13-22; DTX-046.0027-.0028.) As stated in an internal Vifor document titled "PA 21 Milestones" authored by Peter Geisser (a named inventor of the prior art '442 patent), Vifor had a "definitive stop" of the PA21 project "due to high production cost" in 2001. (Tr. (Mulhern) 627:13-628:7; DTX-046.0027.) Vifor "rejuvenated" PA21's development three years later in 2004. (Tr. (Mulhern) 628:8-12; DTX-046.0028.)

c. Unclaimed Features Drove Velphoro Sales

293. Factors unrelated to the asserted claims, like Vifor's marketing strategies and tactics, have contributed significantly to the marketplace performance of Velphoro. (Tr. (McDuff) 747:15-24; *see generally id.* at 746:24-748:1.)

294. Vifor's marketing efforts unrelated to the alleged patented benefits contributed more strongly to demand for Velphoro, as compared to the features that Vifor points to in this case. (Tr. (McDuff) 746:24-748:6.) Based on market research comparing Velphoro and Auryxia, Vifor acknowledged that "Auryxia should end up being the more successful product than Velphoro." (DTX-330.0019; Tr. (Mulhern) 623:3-11.) Vifor undertook marketing efforts, including its "FMC Medical Office Initiative" in 2018, to "blunt[] this otherwise apparent superiority of Auryxia in the marketplace." (Tr. (Mulhern) 623:12-16; DTX-330.0019.) As Dr. McDuff explained, Vifor's marketing efforts included pushing Velphoro in its own dialysis centers. (Tr. (McDuff) 747:20-748:1.)

4. No Nexus

295. Dr. McDuff concluded that there was no nexus between Velphoro and the asserted claims based on his extensive review of Vifor's internal business records, deposition testimony, and technical expert opinions. (Tr. (McDuff) 744:16-20.)

296. Ms. Mulhern is not a lawyer nor an expert in patent law, medicine, science, or chemistry. (Tr. (Mulhern) 591:13-20.)

297. There is no nexus between the alleged novel aspects of the asserted claims and the alleged commercial success of Velphoro. (Tr. (McDuff) 743:15-744:20, 748:2-6.) There is likewise no nexus between these alleged novel aspects and the alleged unexpected results or long-felt but unmet need. (Tr. (Chambliss) 739:16-740:3.)

298. Dr. Rastogi opined that there were three alleged benefits of Velphoro: (1) efficacy, which relates to low iron release and reduced pill burden; (2) "enhanced ease of administration," which included size, chewability, crushability, and palatability; and (3) improved safety due to its low iron release rate, decreased toxicity concerns, and lack of gastrointestinal issues. (Tr. (Rastogi) 514:17-518:1, 520:1-10; (Mulhern) 580:1-18, 583:23-584:4.)

299. Ms. Mulhern relied only on Dr. Rastogi's identification of these alleged benefits to determine whether they drove commercial success of Velphoro. (Tr. (Mulhern) 592:6-11.) Ms. Mulhern did not undertake any analysis to determine whether the alleged benefits are connected to a specific asserted claim. (*Id*. at 592:12-19.)

a. No Nexus Between Increased Efficacy and the Asserted Claims

300. Dr. Rastogi opined that one of Velphoro's attributes was its efficacy, specifically as a high-loading dose and having "very little, if any" iron release. (Tr. (Rastogi) 515:2-11.)

301. Dr. Rastogi admitted that "high loading" is not a term that is used in his practice, and that he views this term to be a formulation, rather than clinical, concept. (Tr. (Rastogi) 526:24-527:7.) Dr. Rastogi is not a chemist nor a formulation expert. (*Id*. at 529:2-4.)

302. Dr. Rastogi admitted that none of the asserted claims recited low pill burden. (Tr. (Rastogi) 525:14-20.) Similarly, as Dr. Chambliss confirmed, the claims do not require any flowable powders. (Tr. (Chambliss) 739:16-740:3.)

303. Vifor's experts characterized the mixture of native and pregelatinized starches as the component responsible for Velphoro's alleged decreased pill burden. (Tr. (Rastogi) 528:17-591:1; (Williams) 719:23-721:9.) Drs. Chofflon and Philipp confirmed that the only difference in composition between PA21-1 and PA21-2 was the inclusion of pregelatinized starch in PA21-2, which became Velphoro. (Tr. 235:21-24, 271:3-16.) Dr. Chofflon also confirmed that the addition of pregelatinized starch was the reason Vifor was able to formulate PA21-2 as a high-load tablet and reduce pill burden. (*Id*. at 271:8-16, 271:21-24.) In fact, Dr. Chofflon characterized this addition of pregelatinized starch as "something important." (*Id*. at 271:17-20.)

304. However, claim 36, which is not asserted, is the only claim that requires a specific starch. (Tr. (Chambliss) 380:16-25, (Rastogi) 530:12-14.) As Dr. Chambliss testified, the asserted claims do not recite any requirement for pre-gelatinized starch, even though it is important to the

alleged invention. (Tr. 380:16-25.)

305. Claim 30 is the only claim that requires a specific iron release. (Tr. (Rastogi) 525:24-526:1.) Whereas Ms. Mulhern stated she relied upon Dr. Rastogi's testimony for her assumption that a nexus exists between Velphoro and asserted claims, Dr. Rastogi stated that he "was not asked to opine on claim 30." (*Id*. at 530:5-6.)

306. Velphoro's alleged "higher efficacy" and "low iron release" are due to its stabilized API. (Tr. (Chambliss) 289:6-290:4; (Rastogi) 515:2-515:24, 551:13-18, *see also* (McDuff) 743:15-744:5, 747:17-24.) The evidence showed that the stabilized API was the primary differentiator and driver of demand for Velphoro. (Tr. (McDuff) 743:15-744:5, 747:17-24; *see generally id.* at 746:24:748:1.)

307. Velphoro's stabilized iron oxyhydroxide API was known for years prior to the priority date of the '251 patent and Velphoro's launch. (Tr. (Chambliss) 289:6-290:4; (McDuff) 743:15-744:5, 747:17-24; *see generally id.* at 746:24-748:1.) The '442 patent, which issued in 2001 and expired in 2021, is directed to stabilized oxyhydroxide. (Tr. (Chambliss) 289:6-290:4, (Mulhern) 634:11-14; JTX-003.1 at Abstract, 1:48-52.).

308. Vifor's documents and corporate witness testimony establish that efficacy – not pill burden – was the primary feature sought by prescribers when considering Velphoro. Vifor's corporate representative, Mr. Charles DeLoach, testified that market research concerning phosphate binders showed that efficacy was "the most important factor." (Tr. (DeLoach) 728:6-12.) Mr. DeLoach also testified that efficacy is the "lone attribute" considered by physicians when selecting a phosphate binder. (*Id*. at 728:9-12, 728:13-17; *see also* (Rastogi) 507:20-508:5.) Additionally, Vifor's 2018 Operating Plan showed that prescribing physicians perceived Velphoro to be "interchangeable" with other phosphate binders, including Renvela, Fosrenol, Auryxia, and

calcium acetate. (Tr. (Mulhern) 603:12-25; DTX-777.0018.) Vifor also recognized that "[e]fficacy drives behaviors, pill burden does not." (Tr. (Mulhern) 604:20-605:8; DTX-777.0018.) In fact, in 2018, Vifor discarded its marketing message focused on pill burden, and shifted its promotional campaign to focus on efficacy. (DTX-324.0013; Tr. (McDuff) 747:2-8.)

309. Velphoro's minimal iron release did not drive demand or sales for Velphoro. (Tr. (McDuff) 747:15-24.) If anything, this feature diminished Velphoro's commercial success. While referencing a fact sheet on iron published by the National Institutes of Health, Dr. Fadem explained that different types of patients have iron deficiencies and anemia, including kidney patients. (Tr. (Fadem) 219:8-220:12; DTX-134.0007-.0011.) As Dr. Rastogi acknowledged, many CKD patients – the target market of Velphoro – are iron deficient, and free iron can actually help in some patients. (Tr. (Rastogi) 132:24-133:10; DTX-300.0019; DTX-500.0002.)

310. While Auryxia and Velphoro are both iron-based binders, Auryxia – unlike Velphoro – also provided free iron. (Tr. (Rastogi) 133:3-10; (Mulhern) 582:25-583:6.) Auryxia had a second indication for treatment of iron deficiency anemia in patients with CKD and on dialysis. (Tr. (Mulhern) 624:11-24.) When considering Auryxia's acquisition as part of "Project Apple," Vifor acknowledged that this second indication gave Auryxia a "compelling dual effect" for treating additional patients and differentiated Auryxia. (Tr. (Mulhern) 625:20-626:16; DTX-500.0032.) Vifor's internal documents also predicted that "Auryxia should end up being the more successful product than Velphoro." (Tr. (Mulhern) 623:3-16; DTX-330.0019.) As Ms. Mulhern's data showed, despite launching nine months later than Velphoro, Auryxia had a higher prescription share and cumulative average prescription share than Velphoro by 2019. (Tr. (Mulhern) 621:12-622:5, 622:13-23; DTX-313-M.)

b. No Nexus Between "Enhanced Ease of Administration" and the Asserted Claims

311. Chewability is not a feature claimed by asserted claims 29, 30, or 56. (JTX-0001.9-.10; Tr. (Rastogi) 524:5-10, 524:15-22.) Drs. Rastogi and Williams both admitted that only claim 33 requires chewable tablets. (Tr. (Rastogi) 524:1-10; (Williams) 701:3-5; (Chambliss) 739:16-25.) Dr. Rastogi stated that he had not been asked to opine on claim 33. (Tr. (Rastogi) 524:11-14, 530:7-11.)

312. Palatability and taste are not features claimed by any of the asserted claims. (Tr. (Rastogi) 524:15-21; (Williams) 701:12-14; (Chambliss) 739:16-740:3.) As Dr. Rastogi admitted, none of the asserted claims require improved palatability, a pleasant taste, or the ability to be "easily chewed." (Tr. (Rastogi) 524:19-525:10; (Chambliss) 739:16-740:3.)

313. Dr. Rastogi also alleged that Velphoro's enhanced ease of administration led to increased compliance. (Tr. (Rastogi) 516:6-20.) But he admitted that patient adherence was not required by the asserted claims. (*Id*. at 523:14-16, 523:20-21.)

314. Dr. Rastogi further mentioned Velphoro's "reasonabl[e] size[]" as an alleged benefit. (Tr. (Rastogi) 516:6-11.) Yet, none of the asserted claims recited a chewable tablet with any specific size. (*Id*. at 525:11-20; (Chambliss) 739:16-740:3; (Williams) 701:15-17.) Moreover, Vifor's experts attributed Velphoro's pill size to its mixture of pregelatinized and native starch, which is not a claimed feature. (Tr. (Rastogi) 528:17-529:1; (Williams) 719:23-721:9.)

315. Chewable and crushable phosphate binders were known in the art and commercially available prior to Velphoro's launch and prior to 2007. (Tr. (Rastogi) 535:19-24, 536:5-9; (Fadem) 731:15-732:2; (Chambliss) 738:17-739:15.) For example, lanthanum was a chewable and crushable tablet. (Tr. (Rastogi) 535:19-21; (Fadem) 296:1-13; (Mulhern) 598:13-15; DTX-729.0006; JTX-0004.6 at 1:35-63.) Likewise, calcium carbonate was a chewable tablet. (Tr. (Rastogi) 535:22-24.) Dr. Chambliss also cited prior art that disclosed chewable tablets for the

treatment of hyperphosphatemia. (Tr. (Chambliss) 296:1-13.)

316. Dr. Rastogi attempted to discount these prior art chewable formulations by emphasizing his concern that patients with "poor dentition" would have difficulty chewing them. (*See* Tr. (Rastogi) 505:24-506:9 (asserting that lanthanum is "difficult to chew" and a concern for "patients [who] have poor dentition"), 516:11-15 (comparing Velphoro to lanthanum and stating that Velphoro is "easy to chew.").) However, none of the asserted claims require a certain ease of chewing. (JTX-0001.9-.10; *see also* Tr. (Rastogi) 516:11-13 (stating that Velphoro is "easy to chew as compared to lanthanum").) As Dr. Williams admitted, the asserted claims are silent on the hardness of formulation. (Tr. (Williams) 701:9-11.)

317. Dr. Fadem confirmed lanthanum's chewability and testified that he had never had any problems concerning chewability or broken teeth with respect to his patients' (and his own) use of lanthanum throughout his 40 years of clinical practice. (Tr. (Fadem) 736:25-737:5.) Even if a patient with poor dentition could not chew lanthanum, as Dr. Rastogi admitted, the phosphate binder could be crushed for administration. (Tr. (Rastogi) 544:20-545:2.)

318. Ms. Mulhern relied upon Dr. Rastogi's identification of Velphoro's "palatable taste and feel," chewability and crushability as features that drive the alleged commercial success of Velphoro. (Tr. (Mulhern) 580:1-18, 581:7-14, 608:9-13.) Rather than driving demand, Velphoro's chewability, crushability, and palatability negatively impacted the demand. (Tr. (McDuff) 747:9-14.) For example, a 2018 report from Fresenius Medical Care, which Ms. Mulhern failed to consider, showed that prescribing physicians considered Velphoro's taste and chewable formulation to be the second and third largest challenges for maintaining long-term Velphoro therapy – i.e., compliance. (Tr. (Mulhern) 608:14-18, 609:2-12, 610:20-611:1, 611:14-19, 612:17-22; DTX-532.0004.) Vifor also noted in its internal market research that taste, texture and

formulation was a "major problem for Velphoro discontinuation" for 40% of physicians, who comprise the relevant market. (Tr. (Mulhern) 613:5-9; DTX-330.0013.) As Vifor's data showed, not only did 43% of physicians report the taste and texture of the product to be the main barrier to increased Velphoro uptake, but 39% of physicians also reported Velphoro's chewable nature to be a barrier for uptake. (DTX-330.0013.) Moreover, Vifor's research emphasized physician feedback that patients preferred PhosLo to Velphoro because Velphoro turned their mouths black. (Tr. (Mulhern) 613:17-614:2; DTX-330.0013.) This report also highlighted that patients did not like the large size of the Velphoro pill. (DTX-330.0013; Tr. (Mulhern) 613:10-16.)

c. No Nexus Between Improved Safety and the Asserted Claims

319. Dr. Rastogi admitted that the asserted claims did not recite any improved safety over other the prior art. (Tr. (Rastogi) 523:22-25.) Dr. Rastogi also opined that an "important" and "significant" safety feature of Velphoro was the lack of any gastrointestinal issues. (Tr. (Rastogi) 520:1-8.)

320. There is no nexus between Dr. Rastogi's emphasis on improved gastrointestinal tolerance and the asserted claims. (Tr. (Chambliss) 739:16-19; (Fadem) 730:17-732:2.) As Dr. Rastogi admitted, none of the asserted claims require a well-tolerated product. (Tr. (Rastogi) 523:9-13.) Dr. Rastogi also admitted that the claims did not require any improved safety. (*Id*. at 523:22-25.) Additionally, safe phosphate binders such as sevelamer and lanthanum were already known in the art. (*See, e.g.,* Tr. (Rastogi) 534:9-15, 535:7-18, 540:19-541:2, (Fadem) 729:20-730:3.; DTX-777.0018.)

321. Velphoro's low iron release was also disadvantage for total revenues and prescription share in the phosphate binder market. For example, as compared to Auryxia, which had a second indication for treating iron deficiency anemia by providing free iron, Velphoro had lower total revenues and prescriptions. (Tr. (Rastogi) 133:3-10; (Mulhern) 624:11-625:10.) Vifor

characterized Auryxia's release of free iron as providing a "compelling dual effect." (Tr. (Mulhern) 624:22-626:16; DTX-500.0032.) It also predicted that Auryxia would be more successful than Velphoro. (Tr. (Mulhern) 623:3-16; DTX-330.0019.) By 2019, Auryxia had a higher prescription share and cumulative average prescription share than Velphoro. (Tr. (Mulhern) 621:12-622:5, 622:13-23; DTX-313-M.)

322. Moreover, Velphoro's alleged reduced gastrointestinal issues did not drive demand. An article relied upon by Ms. Mulhern, *inter alia*, the disadvantages of six commercially available phosphorus binders but highlighted "gastrointestinal side effects" as a disadvantage only with respect to Velphoro. (DTX-729.0006; Tr. (Mulhern) 597:10-18, 599:17-19.) Likewise, an article relied upon by Dr. Rastogi stated that "gastrointestinal tolerance" remained an "unsolved problem" after Velphoro's launch. (DTX-1019.0011; Tr. (Rastogi) 547:13-548:13.)

5. '442 Patent Claimed the API and Was a Blocking Patent

323. The '442 patent served as a blocking patent and limits the relevance of Vifor's alleged secondary considerations. (Tr. (McDuff) 744:6-15, 745:21-746:19.)

324. The '442 patent is listed in the FDA Orange Book for Velphoro. (Tr. (Chambliss) 289:6-16.) This listing provided notice to others that this patent covered Velphoro. (*Id.*)

325. Compound patents like the '442 patent provide value to a pharmaceutical company by conferring exclusivity associated with the use of that compound throughout the patent's life. (Tr. (Mulhern) 633:13-18; (McDuff) 745:21-746:19, 744:6-15.)

326. Vifor characterized the '442 patent as a "basic compound patent" and one of three bases of protection for Velphoro. (Tr. (Mulhern) 636:6-16; (McDuff) 745:7-12, 745:20-22; DTX-321.0002.) Vifor expected that the '442 patent would provide "market exclusivity" for Velphoro through the '442 patent term, as it illustrated in an internal "PA21 Global Filing Strategy" presentation dated July 18, 2013. (DTX-321.0003; Tr. (Mulhern) 636:4-637:8; (McDuff) 746:8-

13, 746:21-23.) The ’442 patent, which issued in 2001, had a patent term that started six years before the priority date of the ’251 patent, thus serving as a block to other competitors who may have sought to formulate a product with the same compound as Velphoro. (Tr. (McDuff) 745:21-746:19.)

327. As the market realities demonstrate, no other iron oxyhydroxide products entered the market during the term of the ’442 patent. (Tr. (McDuff) 745:25-746:19.) In fact, when seeking to market generic versions of Velphoro, both Lupin and Teva did not challenge the ’442 patent, instead filing Paragraph III certifications to this patent and waiting until its expiration to enter the market. (*Id*. at 746:13-16.)

328. As a compound patent, the ’442 patent deterred others from making, developing, and marketing a sucroferric oxyhydroxide formulation. (Tr. (McDuff) 745:21-746:19, 744:6-15; (Mulhern) 634:15-19.) It is undisputed that the ’442 patent would have disincentivized a pharmaceutical company from making a product with beta-iron oxyhydroxide. (Tr. (McDuff) 745:24-746:19; (Mulhern) 634:15-21.) Ms. Mulhern also agreed that the ’442 patent would have blocked a competitor from entering the market with a product having the beta form of iron oxyhydroxide. (Tr. (Mulhern) at 635:11-23.)

VII. IF ASSERTED CLAIMS 29 AND 30 ARE NOT OBVIOUS UNDER 35 U.S.C. § 103, THEY LACK ENABLEMENT UNDER 35 U.S.C. § 112

329. The ’251 patent does not provide examples, clinical data, guidance on assessment, or control and variation instructions regarding “essentially non-bioabsorbable.” (Tr. (Chambliss) 376:22-378:4)

330. Experts for both parties agreed that the ’251 patent did not provide “any guidance” or working examples as to what constitutes a “clinically significant” amount. (Tr. (Rastogi) 121:19-23; (Chambliss) 327:5-16.) Experts for both parties testified that that numerous factors

could affect what would be considered a “clinically significant” amount of absorption, that such factors generally vary from patient to patient, that such factors would be unpredictable to a POSA absent *in vivo* testing of each patient. (Tr. 121:19-23, 122:22-124:2, 125:11-16, 134:25-136:3, 218:16-221:5; DTX-134.0006-.0015; DTX-67.200.)

331. Plaintiffs clinical expert, Dr. Rastogi, testified that the ’251 patent does not indicate what “clinically significant amount” means. (Tr. 121:19-23.) Dr. Rastogi also testified that *in vitro* testing cannot provide information as to whether iron oxyhydroxide is absorbed by the human body in a clinically significant amount. (Tr. 125:11-16.) Dr. Rastogi also testified that, even if *in vitro* testing provided some information, a POSA would want to perform *in vivo* testing to determine whether it is absorbed in a clinically significant amount. (Tr. 123:22-124:2, Tr. 114:5-6.) Dr. Rastogi also testified that what may be “clinically significant” for one patient may not be “clinically significant” for another. (Tr. 134:25-136:3.)

332. Until a product is tested for *in vivo* absorption, it is “impossible” to know whether absorption is clinically significant. (Tr. 218:16-219:5.)

333. Dr. Rastogi did not know whether differences in the type of iron oxyhydroxide can have an impact on iron absorption. (Tr. at 127:5-11.) Dr. Rastogi is not a chemist and is not qualified to opine on this testing. (Tr. at 127:12-128:10.) Dr. Rastogi did not know whether the use of a different disintegrant would affect bioabsorbability. (Tr. at 127:18-128:10.)

334. Bioabsorption of iron or iron oxyhydroxide can vary patient to patient, and various individual patient factors can affect whether the amount of iron absorbed by a human body is clinically significant. (Tr. (Fadem) 220:17-19, 220:24-221:5; DTX-134; *see also* Tr. at 219:8-19, 219:24-220:3, 220:20-23.)

335. The ’251 patent says very little about iron release. (Tr. (Chambliss) 327:17-18.)

The ’251 patent does not disclose that the grade of pregelatinized starch matters with respect to the release rate. (Tr. 381:25-382:3.) There is no indication in the ’251 patent that the characteristics of the pregelatinized starch used affect drug release. (Tr. 383:23-384:4.) The ’251 patent only disclosed that the pregelatinized starch brand Lycatab may be used. (Tr. 381:6-10.) Lycatab could describe more than one specific grade of pregelatinized starch. (Tr. 382:9-15.)

336. The ’251 patent does not provide any guidance regarding how the source and type of starch would impact the iron release rate for sucroferric oxy-hydroxide products absent testing of each product. (Tr. 377:19-378:4.) To the extent the source and type of starch would impact the release rate, the level of experimentation that would be required of a POSA in order to practice the full scope of these claims would be undue. (Tr. 327:11-328:2, 377:19-378:4, 378:11-386:7, PTX-597.7.) There is no way for a person of skill in the art to know whether the composition they make will meet the essentially non-bioabsorbable limitation aside from trial and error with suppliers, grades of starch, and types of starch. (Tr. 378:17-24.)

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